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**PATENT APPLICATION TRANSMITTAL LETTER**  
(Large Entity)Docket No.  
**BPC073**TO THE ASSISTANT COMMISSIONER FOR PATENTS

Transmitted herewith for filing under 35 U.S.C. 111 and 37 C.F.R. 1.53 is the patent application of:

**Michael Chorev, Zheng Xin Dong and Michael Rosenblatt**For: **PTH2 Receptor Selective Compounds**

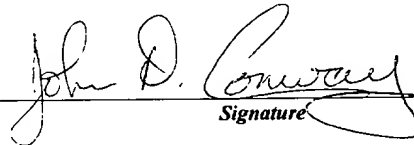
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Docket No.

BPC073

Applicant(s):

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Invention: PTH2 Receptor Selective Compounds

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Patent  
BPC073

**NON-PROVISIONAL APPLICATION  
UNDER 37 CFR 1.53(b)(1)**

**TITLE: PTH2 RECEPTOR SELECTIVE COMPOUNDS**

**APPLICANTS: M. CHOREV, Z. X. DONG AND M. ROSENBLATT**

**EXPRESS MAIL LABEL NO. EI996876136US**

**PTH2 RECEPTOR SELECTIVE COMPOUNDS**

**Statement as to Government Funding**

5 This invention was supported in part by Government funding, NIDDK Research Grant DK-4790, and the Government, therefore, may have certain rights in the invention.

**Background of the Art**

10 This invention relates to a series of PTH and PTHrP analogues that selectively bind to PTH2 receptors and as such may be useful in treating abnormal CNS functions; abnormal pancreatic functions; divergence from normal mineral metabolism and homeostasis; male infertility; regulation of abnormal blood pressure; and hypothalamic disease, to name a few potential uses.

15 An alternate human parathyroid hormone (PTH) receptor, designated as PTH2 receptor, has been identified in rat and human brain. This receptor is selectively activated by PTH-(1-34), but not PTH-related protein PTHrP-(1-34), which has the same calcium-mobilizing activities as PTH-(1-34). Both PTH and PTHrP share a common G protein-coupled receptor, termed the PTH/PTHrP receptor. The PTH2 receptor is localized predominantly in the brain and pancreas, in contrast to PTH/PTHrP receptor, which is primarily localized in bone and the kidney, the principal target tissue for PTH action.

20 Parathyroid hormone (PTH) is the principal physiological regulator of calcium levels in the blood (Chorev, M., Rosenblatt, M., 1994, Structure function analysis of parathyroid hormone and parathyroid hormone-related protein, Bilezikian, J.P., Marcus, R., Levine, M., (eds) The Parathyroids: Basic and Clinical Concepts. Raven Press, New York, pp 139-156; Juppner, H., et al., 1991, Science, 254:1024-1026; and Martin, T.J., et al., 1991, Crit. Rev. Biochem. Mol. Biol. 26:377-395). PTH-related protein (PTHrP) was originally identified as the agent responsible for the paraneoplastic syndrome of humoral hypercalcemia of malignancy (Suva, L.J., et al., 1987, Science, 237:893-896 and Orloff, J.J., et al., 1994, Endocrinol. Rev. 15:40-60). PTH and PTHrP are products of distinct, yet evolutionary-related genes. PTH and PTHrP show sequence similarities only in the N-terminal 13 amino acids, 8 of which are identical (Abou-Samra AB, et al., 1992, Proc. Natl. Sci. Acad. USA, 89 2732-2736). However, the expression pattern and physiological role of these two molecules are remarkably different. PTH has a highly restricted pattern of expression and acts as a classical endocrine hormone, whereas PTHrP is expressed in a wide variety of normal

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tissues and functions in a predominantly autocrine/paracrine fashion (Urena, P., et al., 1993, *Endocrinology*, 133:617-623; Lee, K., et al., 1995, *Endocrinology*, 136:453-463; and Martin, T.J., et al., 1995, *Miner. Electrolyte Metab.*, 21:123-128). More recently, PTHrP has been shown to play a fundamental role in embryonic differentiation of bone and cartilage development.

PTH and PTHrP exert their wide-ranging effects via a common receptor located on the surface of target cells (Juppner, H., et al., 1988, *J. Biol. Chem.*, 263:1071-1078, Shigeno, C., et al., 1988, *J. Biol. Chem.*, 263:18369-18377). The PTH/PTHrP receptor is a member of a subfamily of G protein-coupled receptor superfamily, which includes the receptors for glucagon, growth hormone-releasing hormone (GHRH), vasoactive intestinal peptide (VIP), glucagon-like peptide 1 (GLP-1), gastric inhibitory polypeptide (GIP), secretin, pituitary adenylate cyclase-activating polypeptide (PACAP), calcitonin, and corticotropin-releasing factor (CRF) (Segre, G., et al., 1993, *Trends Endocrinol. Metab.* 4:309-314). The PTH/PTHrP receptor recognizes the N-terminal 1-34 regions of both ligands (Schipani, E., et al., 1993, *Endocrinology*, 132:2157-2165) and is particularly abundant in classical PTH target tissues such as bone and kidney (Urena, P., et al., 1993 *Endocrinology*, 133:35-38). Ligand binding to the PTH/PTHrP receptor can activate at least two signaling pathways; the adenylyl cyclase-cAMP-protein kinase A pathway (Partridge, NC, et al., 1981, *Endocrinology* 108 220-225), and the inositol trisphosphate-cytosolic calcium-protein kinase C pathway (Abou-Samra, A-B., et al., 1989, *Endocrinology* 124:1107-1113).

An homologous receptor for PTH, designated the PTH2 receptor, has been identified and partially characterized (Behar, V., et al., 1996, *Endocrinology*, 137 2748-2757; Gardella, T.J., et al., 1996, *The J. Biol. Chem.*, 271:19888-19893; Behar, V. et al., 1996, *Endocrinology*, 137:4217-4224; and Usdin, T.B., et al., 1997, *Endocrinology*, 138:831-834). Amongst the seven transmembrane G protein-coupled receptors, the PTH2 receptor is most similar in sequence to the PTH/PTHrP receptor (51% of the amino acid sequence identify). Interestingly, PTH2 receptor mRNA is not detected in bone or osteosarcoma cell lines, but is expressed in a number of tissues including the exocrine pancreas, lung, heart, vasculature, and epididymis, and is most abundant in the brain (Usdin, T.B., et al., 1996, *Endocrinology*, 137:4285-4297). Unlike the PTH/PTHrP receptor, which binds and is activated by both PTH-(1-34) and PTHrP-(1-34), the PTH2 receptor binds and is activated only by PTH-(1-34). PTHrP(7-34) was found to recognize PTH2 receptor and weakly activate it. Moreover, His<sup>5</sup> in PTHrP was identified as the "specificity

switch" for the PTH2 receptor. Swapping a single amino acid, His<sup>5</sup> from PTHrP, with Ile<sup>5</sup> from PTH, resulted in a PTHrP analogue, Ile<sup>5</sup>-PTHrP-(1-34)NH<sub>2</sub>, which acts as a PTH-2 receptor agonist. Hence, the single amino acid switch converts inactive PTHrP into a potent PTH2 receptor agonist. But while [Ile<sup>5</sup>]PTHrP binds and activates both receptors, PTH/PTHrP and PTH2, it is not a selective PTH2 agonist. In transient heterologous (with respect to species) expression systems, others have found an additional contribution to hPTH2 receptor selectivity by Trp<sup>23</sup> (Gardella et al., JBC 1996, 271:19888-19893). Like the PTH/PTHrP receptor, PTH binding leads to PTH2 receptor-mediated activation of both cAMP and [Ca<sup>2+</sup>] intracellular signaling pathways.

The physiological function of the PTH2 receptor because of its high abundance and distribution in the brain suggests that it may act as a neurotransmitter receptor. PTH has been found in the central nervous system (CNS) (Harvey, S., et al., 1993, J. Endocrinol. 139:353-361), therefore, it is possible that endogenous PTH2 receptor specific ligands, which are distinct from PTH, do exist in the CNS. Recently, Usdin reported the isolation of "PTH2 receptor binding activity" from the hypothalamus which was immunologically distinct from PTH.

PCT Application Number PCT/US97/13360, published as PCT Publication Number WO 98/04591, discloses the use of certain PTHrP analogs which are PTH2 receptor agonists or antagonists

U.S. Patent No. 5,723,577, issued March 3, 1998, discloses certain PTH and PTHrP analogues. U.S. Application Nos. 08/779,768 and 08/813,534, filed January 7, 1997 and March 7, 1997, respectively, disclose further PTH and PTHrP analogs.

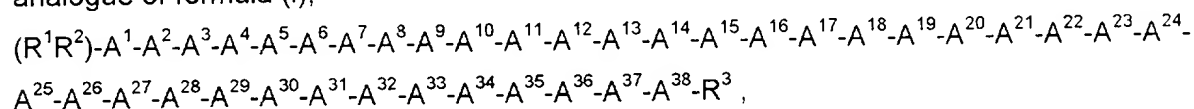
The development of specific ligands which activate the PTH2 receptor but not the PTH/PTHrP receptor, would be highly useful in defining the physiological roles of the PTH2 receptor and its potential involvement in certain pathological states. We have discovered a series of PTH2 receptor-selective PTH analogues which interact selectively with the human PTH2 receptor and are practically devoid of PTH/PTHrP receptor interaction. The compounds of the present invention are not only selective toward a receptor subtype but also signal specifically through the stimulation of [Ca<sup>2+</sup>]<sub>i</sub> transients. Therefore, the compounds of the present invention are receptor subtype and signaling pathway selective.

### **Summary of the Invention**

In one aspect, this invention provides a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof that selectively binds to the PTH2 receptor. A

preferred PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof is where the analogue is a selective PTH2 receptor agonist. Another preferred PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof is where the analogue is a selective PTH2 receptor antagonist.

- 5 A more preferred PTH analogue that selectively binds to the PTH2 receptor is an analogue of formula (I),



(I)

- 10 or a pharmaceutically-acceptable salt thereof wherein

A<sup>1</sup> is a hydrophilic or a lipophilic amino acid;

A<sup>2</sup> is a lipophilic amino acid;

A<sup>3</sup> is a hydrophilic or a lipophilic amino acid;

A<sup>4</sup> is a hydrophilic amino acid.

- 15 A<sup>5</sup> is a hydrophilic or a lipophilic amino acid;

A<sup>6</sup> is a hydrophilic amino acid or is deleted;

A<sup>7</sup> is a hydrophilic or a lipophilic amino acid or is deleted;

A<sup>8</sup> is a lipophilic amino acid or is deleted;

A<sup>9</sup> is a hydrophilic amino acid or is deleted;

- 20 A<sup>10</sup> is a hydrophilic amino acid or is deleted;

A<sup>11</sup> is a hydrophilic or a lipophilic amino acid or is deleted;

A<sup>12</sup> is a hydrophilic or a lipophilic amino acid or is deleted;

A<sup>13</sup> is a hydrophilic amino acid;

A<sup>14</sup> is a hydrophilic amino acid or is deleted;

- 25 A<sup>15</sup> is a lipophilic amino acid or is deleted;

A<sup>16</sup> is a hydrophilic or a lipophilic amino acid or is deleted;

A<sup>17</sup> is a hydrophilic or a lipophilic amino acid or is deleted;

A<sup>18</sup> is a lipophilic amino acid or is deleted;

A<sup>19</sup> is a hydrophilic or a lipophilic amino acid or is deleted;

- 30 A<sup>20</sup> is a hydrophilic amino acid or is deleted;

A<sup>21</sup> is a hydrophilic or a lipophilic amino acid or is deleted;

A<sup>22</sup> is a lipophilic or a hydrophilic amino acid or is deleted;

A<sup>23</sup> is a hydrophilic or a lipophilic amino acid;

A<sup>24</sup> is a hydrophilic or a lipophilic amino acid;

A<sup>25</sup> is a hydrophilic amino acid;

A<sup>26</sup> is a hydrophilic amino acid;

A<sup>27</sup> is a lipophilic or a hydrophilic amino acid;

5 A<sup>28</sup> is a lipophilic amino acid;

A<sup>29</sup> is a lipophilic or a hydrophilic amino acid;

A<sup>30</sup> is a hydrophilic or a lipophilic amino acid;

A<sup>31</sup> is a lipophilic or a hydrophilic amino acid or is deleted;

A<sup>32</sup> is a hydrophilic amino acid or is deleted;

10 A<sup>33</sup> is a hydrophilic amino acid or is deleted;

A<sup>34</sup> is a lipophilic amino acid or is deleted;

A<sup>35</sup> is a lipophilic amino acid or is deleted;

A<sup>36</sup> is a lipophilic or a hydrophilic amino acid or is deleted;

A<sup>37</sup> is a lipophilic amino acid or is deleted;

15 A<sup>38</sup> is a lipophilic or a hydrophilic amino acid or is deleted;

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl-(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

20 or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl; and

R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1-30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1-30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

25 provided that the compound is not PTH(1-34)R<sup>3</sup>, PTH(1-35)R<sup>3</sup>, PTH(1-36)R<sup>3</sup>, PTH(1-37)R<sup>3</sup>, or PTH(1-38)R<sup>3</sup>.

Another preferred group of PTH analogues that selectively binds to the PTH<sub>2</sub> receptor is an analogue of formula (II),

(R<sup>1</sup>R<sup>2</sup>)-A<sup>1</sup>-A<sup>2</sup>-A<sup>3</sup>-A<sup>4</sup>-A<sup>5</sup>-A<sup>6</sup>-A<sup>7</sup>-A<sup>8</sup>-A<sup>9</sup>-A<sup>10</sup>-A<sup>11</sup>-A<sup>12</sup>-A<sup>13</sup>-A<sup>14</sup>-A<sup>15</sup>-A<sup>16</sup>-A<sup>17</sup>-A<sup>18</sup>-A<sup>19</sup>-A<sup>20</sup>-A<sup>21</sup>-A<sup>22</sup>-A<sup>23</sup>-A<sup>24</sup>-  
A<sup>25</sup>-A<sup>26</sup>-A<sup>27</sup>-A<sup>28</sup>-A<sup>29</sup>-A<sup>30</sup>-A<sup>31</sup>-A<sup>32</sup>-A<sup>33</sup>-A<sup>34</sup>-A<sup>35</sup>-A<sup>36</sup>-A<sup>37</sup>-A<sup>38</sup>-R<sup>3</sup>,

30 (II)

or a pharmaceutically-acceptable salt thereof wherein

A<sup>1</sup> is Ser, Ala, Dap, Thr, Aib or is deleted;

A<sup>2</sup> is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;



- A<sup>3</sup> is Ser, Thr, Aib or is deleted;  
A<sup>4</sup> is Glu, Asp or is deleted;  
A<sup>5</sup> is Leu, Val, Nle, Ile, Cha,  $\beta$ -Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;  
A<sup>6</sup> is Gln, a hydrophilic amino acid or is deleted;  
5 A<sup>7</sup> is Leu, Val, Nle, Ile, Cha,  $\beta$ -Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;  
A<sup>8</sup> is Met, Nva, Leu, Val, Ile, Cha, Acc, Nle, p-X-Phe, Phe,  $\beta$ -Nal, Bpa, a lipophilic amino acid or is deleted;  
A<sup>9</sup> is His, a hydrophilic amino acid or is deleted;  
10 A<sup>10</sup> is Asn, a hydrophilic amino acid or is deleted;  
A<sup>11</sup> is Leu, Val, Nle, Ile, Cha,  $\beta$ -Nal, Trp, Pal, Acc, Phe, p-X-Phe, a hydrophilic amino acid or is deleted;  
A<sup>12</sup> is Gly, Acc, Aib, or is deleted;  
A<sup>13</sup> is Lys, Arg or  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$ ;  
15 A<sup>14</sup> is His or is deleted;  
A<sup>15</sup> is Leu, Val, Nle, Ile, Cha,  $\beta$ -Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;  
A<sup>16</sup> is Ser, Asn, Ala, Aib or is deleted;  
A<sup>17</sup> is Ser, Thr, Aib or is deleted;  
A<sup>18</sup> is Met, Nva, Leu, Val, Ile, Nle, p-X-Phe, Phe,  $\beta$ -Nal, Acc, Cha, Aib or is deleted;  
20 A<sup>19</sup> is Glu, Aib or is deleted;  
A<sup>20</sup> is Arg, Lys,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$  or is deleted;  
A<sup>21</sup> is Val, Leu, Ile, Phe, Nle,  $\beta$ -Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;  
A<sup>22</sup> is Acc, Aib, Glu or is deleted;  
A<sup>23</sup> is Trp, Acc, Phe, p-X-Phe, Aib,  $\beta$ -Nal or Cha;  
25 A<sup>24</sup> is Leu, Acc, Ile, Val, Phe,  $\beta$ -Nal, Nle, Aib, p-X-Phe or Cha;  
A<sup>25</sup> is Arg, Lys or  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$ ;  
A<sup>26</sup> is Arg, Lys or  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$ ;  
A<sup>27</sup> is Lys, Aib, Leu, hArg, Gln, Acc, Arg, Cha, Nle, Ile, Val, Phe,  $\beta$ -Nal, or p-X-Phe, where the Lys is optionally substituted on the  $\epsilon$ -amino group by an acyl group;  
30 A<sup>28</sup> is Leu, Acc, Cha, Ile, Val, Phe, Nle,  $\beta$ -Nal, Aib or p-X-Phe;  
A<sup>29</sup> is Gln, Acc or Aib;  
A<sup>30</sup> is Asp, Lys, Arg or is deleted;

A<sup>31</sup> is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal Aib, p-X-Phe or is deleted;

A<sup>32</sup> is His or is deleted;

A<sup>33</sup> is Asn or is deleted;

A<sup>34</sup> is Phe, Tyr, Amp, Aib, β-Nal, Cha, Nle, Leu, Ile, Acc, p-X-Phe or is deleted;

5 A<sup>35</sup> is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal Aib, p-X-Phe or is deleted;

A<sup>36</sup> is Ala, Val, Aib, Acc, Nva, Abu or is deleted;

A<sup>37</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;

A<sup>38</sup> is Gly, Acc, Aib, or is deleted;

10 where X for each occurrence is independently selected from the group consisting of OH, a halo and CH<sub>3</sub>;

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl-(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

15 or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1-30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1-30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

20 n for each occurrence is independently an integer from 1 to 5; and

R<sup>4</sup> for each occurrence is independently (C<sub>1-C30</sub>)alkyl, (C<sub>1-C30</sub>)acyl or -C((NH)(NH<sub>2</sub>));

provided that the compound is not PTH(1-34)R<sup>3</sup>, PTH(1-35)R<sup>3</sup>, PTH(1-36)R<sup>3</sup>, PTH(1-37)R<sup>3</sup>, or PTH(1-38)R<sup>3</sup>.

In another aspect, this invention provides a PTHrP analogue that selectively binds to the PTH2 receptor of the formula (IV),

(R<sup>1</sup>R<sup>2</sup>)-A<sup>1</sup>-A<sup>2</sup>-A<sup>3</sup>-A<sup>4</sup>-A<sup>5</sup>-A<sup>6</sup>-A<sup>7</sup>-A<sup>8</sup>-A<sup>9</sup>-A<sup>10</sup>-A<sup>11</sup>-A<sup>12</sup>-A<sup>13</sup>-A<sup>14</sup>-A<sup>15</sup>-A<sup>16</sup>-A<sup>17</sup>-A<sup>18</sup>-A<sup>19</sup>-A<sup>20</sup>-A<sup>21</sup>-A<sup>22</sup>-A<sup>23</sup>-A<sup>24</sup>-A<sup>25</sup>-A<sup>26</sup>-A<sup>27</sup>-A<sup>28</sup>-A<sup>29</sup>-A<sup>30</sup>-A<sup>31</sup>-A<sup>32</sup>-A<sup>33</sup>-A<sup>34</sup>-A<sup>35</sup>-A<sup>36</sup>-A<sup>37</sup>-A<sup>38</sup>-R<sup>3</sup>,

(IV)

or a pharmaceutically acceptable salt thereof, wherein

30 A<sup>1</sup> is Ala, Ser, Dap, Thr, Aib or is deleted;

A<sup>2</sup> is Val or is deleted;

A<sup>3</sup> is Ser, Aib, Thr or is deleted;

A<sup>4</sup> is Glu, Asp or is deleted;

A<sup>5</sup> is His, Ile, Acc, Val, Nle, Phe, Leu, p-X-Phe,  $\beta$ -Nal, Aib, Cha or is deleted;

A<sup>6</sup> is Gln, a hydrophilic amino acid or is deleted;

A<sup>7</sup> is Leu, Val, Cha, Nle,  $\beta$ -Nal, Trp, Pal, Acc, Phe, p-X-Phe, Aib, a lipophilic amino acid or is deleted;

5 A<sup>8</sup> is Leu, Met, Acc, Cha, Aib, Nle, Phe, Ile, Val,  $\beta$ -Nal, p-X-Phe, a lipophilic amino acid or is deleted;

A<sup>9</sup> is His, a hydrophilic amino acid or is deleted;

A<sup>10</sup> is Asp, Asn, a hydrophilic amino acid or is deleted;

A<sup>11</sup> is Lys, Arg, Leu, Cha, Aib, p-X-Phe, Ile, Val, Nle, Acc, Phe,  $\beta$ -Nal,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)-$

10 C(O), a lipophilic D-amino acid, a hydrophilic amino acid or is deleted;

A<sup>12</sup> is Gly, Acc, Aib or is deleted;

A<sup>13</sup> is Lys, Arg,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)-\text{C(O)}$  or is deleted;

A<sup>14</sup> is Ser, His or is deleted;

A<sup>15</sup> is Ile, Acc, Cha, Leu, Phe, Nle,  $\beta$ -Nal, Trp, p-X-Phe, Val, Aib or is deleted;

15 A<sup>16</sup> is Gln, Aib or is deleted;

A<sup>17</sup> is Asp, Aib or is deleted;

A<sup>18</sup> is Leu, Aib, Acc, Cha, Phe, Ile, Nle,  $\beta$ -Nal, Val, p-X-Phe or is deleted,

A<sup>19</sup> is Arg, Lys, Aib,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)-\text{C(O)}$  or is deleted;

A<sup>20</sup> is Arg, Lys,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)-\text{C(O)}$  or is deleted;

20 A<sup>21</sup> is Arg, Lys,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)-\text{C(O)}$  or is deleted;

A<sup>22</sup> is Phe, Glu, Aib, Acc, p-X-Phe,  $\beta$ -Nal, Val, Leu, Ile, Nle or Cha;

A<sup>23</sup> is Phe, Leu, Lys, Acc, Cha,  $\beta$ -Nal, Aib, Nle, Ile, p-X-Phe, Val or Trp;

A<sup>24</sup> is Leu, Lys, Acc, Nle, Ile, Val, Phe,  $\beta$ -Nal, Aib, p-X-Phe, Arg or Cha;

A<sup>25</sup> is His, Lys, Aib, Acc, Arg or Glu;

25 A<sup>26</sup> is His, Aib, Acc, Arg or Lys;

A<sup>27</sup> is Leu, Lys, Acc, Arg, Ile, Val, Phe, Aib, Nle,  $\beta$ -Nal, p-X-Phe or Cha;

A<sup>28</sup> is Ile, Leu, Lys, Acc, Cha, Val, Phe, p-X-Phe, Nle,  $\beta$ -Nal, Aib or is deleted;

A<sup>29</sup> is Ala, Glu, Acc, Aib or is deleted;

A<sup>30</sup> is Glu, Leu, Nle, Cha, Aib, Acc, Lys, Arg or is deleted;

30 A<sup>31</sup> is Ile, Leu, Cha, Lys, Acc, Phe, Val, Nle,  $\beta$ -Nal, Arg or is deleted,

A<sup>32</sup> is His or is deleted;

A<sup>33</sup> is Thr, Ser or is deleted;

A<sup>34</sup> is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;

A<sup>35</sup> is Glu, Asp or is deleted;

A<sup>36</sup> is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;

A<sup>37</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

5 A<sup>38</sup> is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl-(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl.

10 or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1-30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1-30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

n for each occurrence is independently an integer from 1 to 5; and

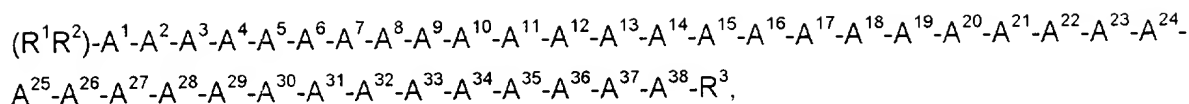
15 R<sup>4</sup> for each occurrence is independently (C<sub>1-C30</sub>)alkyl, (C<sub>1-C30</sub>)acyl or -C((NH)(NH<sub>2</sub>));  
provided that the compound is not PTHrP(1-34)R<sup>3</sup>, PTHrP(1-35)R<sup>3</sup>, PTHrP(1-36)R<sup>3</sup>,  
PTHrP(1-37)R<sup>3</sup> or PTHrP(1-38)R<sup>3</sup>,  
and further provided that the compound is not [Ile<sup>5</sup>, Trp<sup>23</sup>]PTHrP(1-36) or [Trp<sup>23</sup>]PTHrP(1-36).

20 In another aspect, this invention provides a method of selectively binding the PTH2 receptor which comprises administering to a patient in need thereof an effective amount of a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof that selectively binds to a PTH2 receptor.

25 In another aspect, this invention provides a method of selectively eliciting an agonist response from the PTH2 receptor which comprises administering to a patient in need thereof an effective amount of a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof which is a selective PTH2 receptor agonist.

30 In another aspect, this invention provides a method of selectively eliciting an antagonist response from the PTH2 receptor which comprises administering to a patient in need thereof an effective amount of a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof which is a selective PTH2 receptor antagonist.

In yet another aspect, this invention provides a compound of the formula (III),



(III)

or a pharmaceutically-acceptable salt thereof wherein

- 5 A<sup>1</sup> is Ser, Ala, Dap, Thr, Aib or is deleted;  
A<sup>2</sup> is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;  
A<sup>3</sup> is Ser, Thr, Aib or is deleted;  
A<sup>4</sup> is Glu, Asp or is deleted;  
A<sup>5</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;
- 10 A<sup>6</sup> is Gln, a hydrophilic amino acid or is deleted;  
A<sup>7</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;  
A<sup>8</sup> is Met, Nva, Leu, Val, Ile, Cha, Acc, Nle, p-X-Phe, Phe, β-Nal, Bpa, a lipophilic amino acid or is deleted;
- 15 A<sup>9</sup> is His, a hydrophilic amino acid or is deleted;  
A<sup>10</sup> is Asn, a hydrophilic amino acid or is deleted;  
A<sup>11</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a hydrophilic amino acid or is deleted;  
A<sup>12</sup> is Gly, Acc, Aib, or is deleted;
- 20 A<sup>13</sup> is Lys, Arg or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);  
A<sup>14</sup> is His or is deleted;  
A<sup>15</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;  
A<sup>16</sup> is Ser, Asn, Ala, Aib or is deleted;  
A<sup>17</sup> is Ser, Thr, Aib or is deleted;
- 25 A<sup>18</sup> is Met, Nva, Leu, Val, Ile, Nle, p-X-Phe, Phe, β-Nal, Acc, Cha, Aib or is deleted;  
A<sup>19</sup> is Glu, Aib or is deleted;  
A<sup>20</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;  
A<sup>21</sup> is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;  
A<sup>22</sup> is Acc, Aib, Glu or is deleted;
- 30 A<sup>23</sup> is Trp, Acc, Phe, p-X-Phe, Aib, β-Nal or Cha;  
A<sup>24</sup> is Leu, Acc, Ile, Val, Phe, β-Nal, Nle, Aib, p-X-Phe or Cha;  
A<sup>25</sup> is Arg, Lys or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);

A<sup>26</sup> is Arg, Lys or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);

A<sup>27</sup> is Lys, Aib, Leu, hArg, Gln, Acc, Arg, Cha, Nle, Ile, Val, Phe, β-Nal, or p-X-Phe, where the Lys is optionally substituted on the ε-amino group by an acyl group;

A<sup>28</sup> is Leu, Acc, Cha, Ile, Val, Phe, Nle, β-Nal, Aib or p-X-Phe;

5 A<sup>29</sup> is Gln, Acc or Aib;

A<sup>30</sup> is Asp, Lys, Arg or is deleted;

A<sup>31</sup> is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal Aib, p-X-Phe or is deleted;

A<sup>32</sup> is His or is deleted;

A<sup>33</sup> is Asn or is deleted;

10 A<sup>34</sup> is Phe, Tyr, Amp, Aib, β-Nal, Cha, Nle, Leu, Ile, Acc, p-X-Phe or is deleted;

A<sup>35</sup> is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal Aib, p-X-Phe or is deleted;

A<sup>36</sup> is Ala, Val, Aib, Acc, Nva, Abu or is deleted;

A<sup>37</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;

15 A<sup>38</sup> is Gly, Acc, Aib, or is deleted;

where X for each occurrence is independently selected from the group consisting of OH, a halo and CH<sub>3</sub>;

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl-(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

20 or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1-30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1-30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

25 n for each occurrence is independently an integer from 1 to 5; and

R<sup>4</sup> for each occurrence is independently (C<sub>1-C30</sub>)alkyl, (C<sub>1-C30</sub>)acyl or -C((NH)(NH<sub>2</sub>));

provided that when A<sup>8</sup> is not a lipophilic D-amino acid or is not deleted then at least one of A<sup>6</sup>, A<sup>7</sup>, A<sup>9</sup>, A<sup>10</sup>, A<sup>11</sup> and A<sup>12</sup> is a D-amino acid or at least one of A<sup>6</sup>, A<sup>7</sup>, A<sup>9</sup>, A<sup>10</sup>, A<sup>11</sup>, A<sup>12</sup>, A<sup>13</sup>,

30 A<sup>14</sup>, A<sup>15</sup>, A<sup>16</sup>, A<sup>17</sup>, A<sup>18</sup>, A<sup>19</sup>, A<sup>20</sup>, A<sup>21</sup> and A<sup>22</sup> is deleted;

and further provided that when the compound contains a D-amino acid then A<sup>36</sup> is deleted.

A preferred group of compounds of formula (III) are the compounds listed as Examples 1-73, shown hereinbelow. Of the compounds listed as Examples 1-73, the following compounds are preferred: [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH-(1-34)NH<sub>2</sub>, [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH-(1-34)NH<sub>2</sub>, [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH-(1-34)NH<sub>2</sub>, [D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> and [D-Bpa<sup>8</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>.

In yet another aspect, this invention provides a compound of formula (V),  

$$(R^1R^2)-A^1-A^2-A^3-A^4-A^5-A^6-A^7-A^8-A^9-A^{10}-A^{11}-A^{12}-A^{13}-A^{14}-A^{15}-A^{16}-A^{17}-A^{18}-A^{19}-A^{20}-A^{21}-A^{22}-A^{23}-A^{24}-A^{25}-A^{26}-A^{27}-A^{28}-A^{29}-A^{30}-A^{31}-A^{32}-A^{33}-A^{34}-A^{35}-A^{36}-A^{37}-A^{38}-R^3,$$

(V)

or a pharmaceutically acceptable salt thereof, wherein

A<sup>1</sup> is Ala, Ser, Dap, Thr, Aib or is deleted;

A<sup>2</sup> is Val or is deleted;

A<sup>3</sup> is Ser, Aib, Thr or is deleted;

A<sup>4</sup> is Glu, Asp or is deleted;

A<sup>5</sup> is His, Ile, Acc, Val, Nle, Phe, Leu, p-X-Phe, β-Nal, Aib, Cha or is deleted;

A<sup>6</sup> is Gln, a hydrophilic amino acid or is deleted;

A<sup>7</sup> is Leu, Val, Cha, Nle, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, Aib, a lipophilic amino acid or is deleted;

A<sup>8</sup> is Leu, Met, Acc, Cha, Aib, Nle, Phe, Ile, Val, β-Nal, p-X-Phe, a lipophilic amino acid or is deleted;

A<sup>9</sup> is His, a hydrophilic amino acid or is deleted;

A<sup>10</sup> is Asp, Asn, a hydrophilic amino acid or is deleted;

A<sup>11</sup> is Lys, Arg, Leu, Cha, Aib, p-X-Phe, Ile, Val, Nle, Acc, Phe, β-Nal, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O), a lipophilic D-amino acid, a hydrophilic amino acid or is deleted;

A<sup>12</sup> is Gly, Acc, Aib or is deleted;

A<sup>13</sup> is Lys, Arg, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>14</sup> is Ser, His or is deleted;

A<sup>15</sup> is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;

A<sup>16</sup> is Gln, Aib or is deleted;

A<sup>17</sup> is Asp, Aib or is deleted;

A<sup>18</sup> is Leu, Aib, Acc, Cha, Phe, Ile, Nle, β-Nal, Val, p-X-Phe or is deleted.

A<sup>19</sup> is Arg, Lys, Aib, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

- A<sup>20</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;  
A<sup>21</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;  
A<sup>22</sup> is Phe, Glu, Aib, Acc, p-X-Phe, β-Nal, Val, Leu, Ile, Nle or Cha;  
A<sup>23</sup> is Phe, Leu, Lys, Acc, Cha, β-Nal, Aib, Nle, Ile, p-X-Phe, Val or Trp;  
5 A<sup>24</sup> is Leu, Lys, Acc, Nle, Ile, Val, Phe, β-Nal, Aib, p-X-Phe, Arg or Cha;  
A<sup>25</sup> is His, Lys, Aib, Acc, Arg or Glu;  
A<sup>26</sup> is His, Aib, Acc, Arg or Lys;  
A<sup>27</sup> is Leu, Lys, Acc, Arg, Ile, Val, Phe, Aib, Nle, β-Nal, p-X-Phe or Cha;  
A<sup>28</sup> is Ile, Leu, Lys, Acc, Cha, Val, Phe, p-X-Phe, Nle, β-Nal, Aib or is deleted;  
10 A<sup>29</sup> is Ala, Glu, Acc, Aib or is deleted;  
A<sup>30</sup> is Glu, Leu, Nle, Cha, Aib, Acc, Lys, Arg or is deleted;  
A<sup>31</sup> is Ile, Leu, Cha, Lys, Acc, Phe, Val, Nle, β-Nal, Arg or is deleted;  
A<sup>32</sup> is His or is deleted;  
A<sup>33</sup> is Thr, Ser or is deleted;  
15 A<sup>34</sup> is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;  
A<sup>35</sup> is Glu, Asp or is deleted;  
A<sup>36</sup> is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;  
A<sup>37</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;  
A<sup>38</sup> is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;  
20 R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl-(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl, or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;  
25 R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1-30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1-30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;  
n for each occurrence is independently an integer from 1 to 5; and  
R<sup>4</sup> for each occurrence is independently (C<sub>1-30</sub>)alkyl, (C<sub>1-30</sub>)acyl or -C((NH)(NH<sub>2</sub>));  
30 provided that when A<sup>8</sup> is not a lipophilic D-amino acid or is not deleted then at least one of A<sup>6</sup>, A<sup>7</sup>, A<sup>9</sup>, A<sup>10</sup>, A<sup>11</sup> and A<sup>12</sup> is a D-amino acid or at least one of A<sup>6</sup>, A<sup>7</sup>, A<sup>9</sup>, A<sup>10</sup>, A<sup>11</sup>, A<sup>12</sup>, A<sup>13</sup>, A<sup>14</sup>, A<sup>15</sup>, A<sup>16</sup>, A<sup>17</sup>, A<sup>18</sup>, A<sup>19</sup>, A<sup>20</sup>, A<sup>21</sup> and A<sup>22</sup> is deleted.



A preferred group of compounds of formula (V) are the compounds listed as Examples 74-86, shown hereinbelow.

In a further aspect, this invention provides a method of selectively binding the PTH2 receptor which comprises administering to a patient in need thereof an analogue of formula (I), (II) or (III) or a pharmaceutically acceptable salt thereof.

In another aspect, this invention provides a method of selectively binding the PTH2 receptor which comprises administering to a patient in need thereof a compound of formula (III) or (V) or a pharmaceutically acceptable salt thereof. Preferred of the foregoing method is where the compound is selected from Examples 1-73 or Examples 74-86.

In another aspect, this invention is directed to a pharmaceutical composition comprising an analogue of formula (I), (II) or (III) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

In still another aspect, this invention is directed to a pharmaceutical composition comprising a compound of formula (III) or (V) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Preferred is a pharmaceutical composition comprising a compound selected from Examples 1-73 or Examples 74-86.

In still another aspect, this invention is directed to a method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof that selectively binds to the PTH2 receptor, sufficient to inhibit the activation of the PTH2 receptor of said patient. A preferred method of the immediately foregoing method is where said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease. Preferred of each of the immediately foregoing methods is where the analogue is a PTH2 agonist or a PTH2 antagonist.

In another aspect, this invention provides a method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of an analogue of formula (I), (II) or (III), sufficient to inhibit the activation of the PTH2 receptor of said patient. A preferred method of the immediately foregoing method is where said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

In another aspect, this invention is directed to a method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound of formula (III) or (V), sufficient to inhibit the activation of the PTH2 receptor of said patient. A preferred method of the immediately foregoing method is where said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease. Preferred of each of the foregoing methods is where the compound is selected from Examples 1-73 or Examples 74-86.

### Detailed Description

With the exception of the N-terminal amino acid, all abbreviations (e.g. Ala or A<sub>1</sub>) of amino acids in this disclosure stand for the structure of -NH-CH(R)-CO-, wherein R is the side chain of an amino acid (e.g., CH<sub>3</sub> for Ala). For the N-terminal amino acid, the abbreviation stands for the structure of (R<sup>1</sup>R<sup>2</sup>)-N-CH(R)-CO-, wherein R is a side chain of an amino acid and R<sup>1</sup> and R<sup>2</sup> are as defined above. Bpa is p-benzoylphenylalanine. β-Nal, Nle, Dap, Cha, Nva, Amp, Pal, and Aib are the abbreviations of the following α-amino acids: β-(2-naphthyl)alanine, norleucine, α,β-diaminopropionic acid, cyclohexylalanine, norvaline, 4-amino-phenylalanine, β-(3-pyridinyl)alanine and α-aminoisobutyric acid, respectively. What is meant by Acc is an amino acid selected from the group of 1-amino-1-cyclopropanecarboxylic acid; 1-amino-1-cyclobutanecarboxylic acid; 1-amino-1-cyclopentanecarboxylic acid; 1-amino-1-cyclohexanecarboxylic acid; 1-amino-1-cycloheptanecarboxylic acid; 1-amino-1-cyclooctanecarboxylic acid; and 1-amino-1-cyclononanecarboxylic acid. In the above formula, hydroxyalkyl, hydroxyphenylalkyl, and hydroxynaphthylalkyl may contain 1-4 hydroxy substituents. COE<sub>1</sub> stands for -C=O·E<sup>1</sup>. Examples of -C=O·E<sup>1</sup> include, but are not limited to, acetyl and phenylpropionyl. What is meant by "(C<sub>1-12</sub>) hydrocarbon moiety" is an alkyl group, an alkenyl group or an alkynyl group.

What is meant by a "hydrophilic amino acid" is an amino acid having at least one hydrophilic functional group in addition to those required for peptide bond formation, such as: Arg, Asp, Asn, Glu, Gln, Gly, His, Lys, Orn (ornithine), Ser, Thr, β-Ala, Ala, Aad (α-amino adipic acid), β-Aad (β-amino adipic acid), Apm (α-aminopimolic acid), Cit (citrulline), Gla (γ-carboxy-glutamic acid), hArg (homo-Arg), hCit (homo-Cit), hSer (homo-Ser), Dbα (α,γ-

diamino-butyric acid), Dpa ( $\alpha,\beta$ -diaminopropionic acid), Amp (p-amino-phenylalanine), Pal, and their homologues.

What is meant by a "lipophilic amino acid" is an uncharged, aliphatic or aromatic amino acid, such as: Val, Leu, Ile, Pro, Cys, Phe, Met, Trp, Tyr, Cha,  $\beta$ -Nal, Aib, Acc, Ala, Abu ( $\alpha$ -aminobutyric acid), Nle, Nva (norvaline), Bpa (p-benzoyl-phenylalanine), hPhe (homo-Phe), hPro (homo-Pro), 1-Nal( $\beta$ -(1-naphthyl)alanine), 2-Nal ( $\beta$ (2-naphthyl)alanine), Oic (octahydroindode-2-carboxylic acid), Tic (1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid), Pen (penicillamine), Phg (phenylglycine), Tie (t-leucine), p-X-Phe (X= Br, F, I, Cl, CH, phenyl, CN, NO<sub>2</sub>), Tal ( $\beta$ -(2-thienyl)-alanine), and their homologues.

Alanine,  $\beta$ -alanine and sarcosine (Sar) may be considered either a hydrophilic or a lipophilic amino acid.

"Physiologically active truncated homologue or analogue of PTH" refers to a polypeptide having a sequence comprising less than the full complement of amino acids found in PTH.

The full names for other abbreviations used herein are as follows: Boc for t-butyloxycarbonyl, HF for hydrogen fluoride, Fm for formyl, Xan for xanthyl, Bzl for benzyl, Tos for tosyl, DNP for 2,4-dinitrophenyl, DMF for dimethylformamide, DCM for dichloromethane, HBTU for 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate, DIEA for diisopropylethylamine, HOAc for acetic acid, TFA for trifluoroacetic acid, 2CIZ for 2-chlorobenzyloxycarbonyl and OcHex for O-cyclohexyl.

A peptide of this invention is also denoted herein by another format, e.g., [D-Nle<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>, with the substituted amino acids from the natural sequence placed between the set of brackets (e.g., D-Nle<sup>8</sup> for Met<sup>8</sup> in hPTH). The abbreviation hPTH stands for human PTH, and hPTHrP for human PTHrP. The numbers between the parentheses refer to the number of amino acids present in the peptide (e.g., hPTH(1-34) is amino acids 1 through 34 of the peptide sequence for human PTH). The sequences for hPTH(1-34) and hPTHrP(1-34) are listed in Nissenson, et al., Receptor, 3:193 (1993). The designation "NH<sub>2</sub>" in PTH(1-34)NH<sub>2</sub> indicates that the C-terminus of the peptide is amidated. PTH(1-34) means that the C-terminus is the free acid.

The peptides of this invention can be prepared by standard solid phase peptide synthesis. See, e.g., Stewart, J.M., et al., Solid Phase Synthesis (Pierce Chemical Co., 2d ed. 1984). The substituents R<sup>1</sup> and R<sup>2</sup> of the above generic formula may be attached to the free amine of the N-terminal amino acid by standard methods known in the art. For

example, alkyl groups, e.g., (C<sub>1-12</sub>)alkyl, may be attached using reductive alkylation. Hydroxyalkyl groups, e.g., (C<sub>1-12</sub>)hydroxyalkyl, may also be attached using reductive alkylation wherein the free hydroxy group is protected with a t-butyl ester. Acyl groups, e.g., COE<sup>1</sup>, may be attached by coupling the free acid, e.g., E<sup>1</sup>COOH, to the free amine of the N-terminal amino acid by mixing the completed resin with 3 molar equivalents of both the free acid and diisopropylcarbodiimide in methylene chloride for one hour. If the free acid contains a free hydroxy group, e.g., p-hydroxyphenylpropionic acid, then the coupling should be performed with an additional 3 molar equivalents of HOBT.

When R<sup>3</sup> is NH-Y-CH<sub>2</sub>-CONH<sub>2</sub> (Z=CONH<sub>2</sub>), the synthesis of the peptide starts with BocHN-Y-CH<sub>2</sub>-COOH which is coupled to the resin. If R<sup>3</sup> is NH-Y-CH<sub>2</sub>-COOH (Z=COOH) the synthesis of the peptide starts with Boc-HN-Y-CH<sub>2</sub>-COOH which is coupled to PAM resin. When R<sup>3</sup> is OH the first amino acid is coupled to PAM resin.

The compounds of this invention can be tested for binding to the human PTH<sub>2</sub> (hPTH<sub>2</sub>) receptor for the ability to stimulate adenylyl cyclase and/or intracellular calcium transients by the assay described below.

Materials and Methods: Tissue culture media and sera were purchased from Life Technologies (Grand Island, NY), and all tissue culture plastics were obtained from Corning (Corning, NY). Adenosine and 3-isobutyl-1-methyl xanthine (IBMX) were purchased from Research Biochemicals (Natick, MA). Fura-2 acetoxymethyl ester (fura-2/AM) was obtained from Molecular Probes (Eugene, OR), and hPTHrP was purchased from Bachem (Torrance, CA). [<sup>3</sup>H]-Adenine was purchased from New England Nuclear (Boston, MA). Na<sup>125</sup>I was obtained from Amersham Corp. (Arlington Heights, IL). All other analytical grade reagents were purchased from Sigma (St. Louis, MO).

Cell Culture: Human osteosarcoma Saos-2/B-10 cells (American Type Culture Collection, Rockville, MD; ATCC #HTB 85) are maintained in RPMI 1640 medium (Sigma, St. Louis, MO) supplemented with 10% fetal bovine serum (FBS) and 2 mM glutamine at 37°C in a humidified atmosphere of 5% CO<sub>2</sub> in air. The medium is changed every three or four days, and the cells are subcultured every week by trypsinization. Stably transfected HEK-293/BP-16 cells (Beth Israel Deaconess Medical Center-Division of Bone and Mineral Metabolism, Boston, MA), which express the hPTH<sub>2</sub> receptor (160,000 receptors/cell) and stably transfected HEK-293/C-21 cells (Beth Israel Deaconess Medical Center-Division of Bone and Mineral Metabolism, Boston, MA), which express the hPTH/PTHrP receptor, are maintained in DMEM supplemented with 10% FBS at 37°C in a humidified atmosphere of

95% air/5% CO<sub>2</sub>. The medium is changed every 2 days before confluency and every day after confluency. The cells are sub-cultured 1:10 once a week.

Receptor binding assay: Ligand binding is performed using Saos-2/B-10, HEK/C-21 cells or HEK/BP-16 cells using HPLC-purified [<sup>125</sup>I][Nle<sup>8,18</sup>, Tyr<sup>34</sup>]bPTH-(1-34)NH<sub>2</sub> (<sup>125</sup>I-PTH) as radioligand. Saos-2 cells are maintained for four days until they reach confluence. The medium is replaced with 5% FBS in RPMI 1640 medium and incubated for about 2 hrs at room temperature with 10 x 10<sup>4</sup> cpm mono-<sup>125</sup>I-[Nle<sup>8,18</sup>, Tyr<sup>34</sup>(3-<sup>125</sup>I)]bPTH(1-34)NH<sub>2</sub> in the presence of competing peptides of the invention at various concentrations between 10<sup>-11</sup>M to 10<sup>-4</sup> M. The cells are washed four times with ice-cold PBS and lysed with 0.1 M NaOH, and the radioactivity associated with the cells is counted in a scintillation counter. Synthesis of mono-<sup>125</sup>I-[Nle<sup>8,18</sup>, Tyr<sup>34</sup>(3-<sup>125</sup>I)]bPTH(1-34)NH<sub>2</sub> is carried out as described in Goldman, M.E., et al., Endocrinol. 123 1468 (1988).

The binding assay is conducted with various peptides of the invention, and the K<sub>d</sub> value (half maximal inhibition of binding of mono-<sup>125</sup>I-[Nle<sup>8,18</sup>, Tyr<sup>34</sup>(3-<sup>125</sup>I)]bPTH(1-34)NH<sub>2</sub>) for each peptide is calculated

Adenylyl cyclase assay: Adenylyl cyclase assay is performed in Saos-2/B-10 cells, HEK/C21 cells, and HEK/BP-16 cells. The ability of the peptides of the invention to induce a biological response in Saos-2/B-10 cells is measured. More specifically, any stimulation of the adenylyl cyclase is determined by measuring the level of synthesis of cAMP (adenosine 3',5'-monophosphate) as described previously in Rodan, et al., J. Clin. Invest. 72: 1511 (1983) and Goldman, et al., Endocrinol., 123:1468 (1988). Confluent Saos-2/B-10 cells in 24 well plates at 4x10<sup>4</sup> cells/well in RPMI1640 medium containing 10% FBS. Cells are washed twice with Ca<sup>2+</sup> and Mg<sup>2+</sup> free Hanks' balanced salt solution and incubated with 0.5 µCi [<sup>3</sup>H]adenine (26.9 Ci/mmol, New England Nuclear, Boston, MA) in fresh medium at about 37°C for about 2 hrs, and washed twice with Hank's balanced salt solution (Gibco, Gaithersburg, MD). The cells are treated with 1 mM IBMX [isobutylmethyl-xanthine, Sigma, St. Louis, MO] in fresh medium for 15 min, and a peptide to be tested is added to the medium to incubate for about 5 min. The reaction is stopped by the addition of 1.2 M trichloroacetic acid (TCA) (Sigma, St. Louis, MO) followed by sample neutralization with 4 N KOH. cAMP is isolated by the two-column chromatographic method (Salmon, et al., 1974, Anal. Biochem. 58, 541). The radioactivity is counted in a scintillation counter (Liquid Scintillation Counter 2200CA, PACKARD, Downers Grove, IL).

Measurements of  $[Ca^{2+}]_i$ : Measurements of intracellular  $Ca^{2+}$  ( $[Ca^{2+}]_i$ ) are performed in Saos-2/B-10 cells, HEK/C-21 cells and HEK/BP-16 cells. For measurement of  $[Ca^{2+}]_i$ , cells are harvested from 150-cm<sup>2</sup> flasks using HEPES-buffered balanced salt solution containing 0.02% (vol/vol) EDTA. The cell suspension is washed three times with Hanks' Balanced Salt Solution (1 mM  $CaCl_2$ , 118 mM NaCl, 4.6 mM KCl, 10 mM d-glucose, and 20 mM HEPES, pH 7.4), and cells are loaded with fura-2/AM (1 $\mu$ M) for about 40 min at about 37°C. The cell suspension is washed three times with Hanks' Balanced Salt Solution, and fluorescence is measured in a SPEX AR-CM system spectrofluorimeter (SPEX Industries, Edison, NJ). Dual wavelength measurements are performed (excitation wavelengths, 340 and 380 nm; emission wavelength, 505 nm).

$[Ca^{2+}]_i$  is calculated from fura-2 ratios (R) by the equation:  $[Ca^{2+}]_i = K (R - R_{min}) / (R_{max} - R)$ , where  $R_{min}$  and  $R_{max}$  are the ratios (e.g. 340 nm/380 nm) for the minimal or maximal calcium concentration, respectively. K is the product  $K_d(F_0/F_s)$ , where  $K_d$  is the effective dissociation constant (224 nM),  $F_0$  is the intensity of the 380-nm excitation signal in the absence of calcium, and  $F_s$  is the intensity of the 380-nm excitation signal at saturating calcium concentrations. Maximum fluorescence intensity is obtained by permeabilizing the cells with 50  $\mu$ M digitonin in the presence of 1 mM  $CaCl_2$ , and minimal fluorescence intensity is obtained by chelating calcium with 16.6 mM EGTA [pH adjusted to 8.3 with 1M Tris-(hydroxymethyl)aminomethane base]. Addition of vehicle alone (0.1% BSA in PBS) did not change the level of  $[Ca^{2+}]_i$ .

The peptides of this invention can be provided in the form of pharmaceutically acceptable salts. Examples of such salts include, but are not limited to, those formed with organic acids (e.g., acetic, lactic, maleic, citric, malic, ascorbic, succinic, benzoic, methanesulfonic, toluenesulfonic or pamoic acid), inorganic acids (e.g., hydrochloric acid, sulfuric acid, or phosphoric acid), and polymeric acids (e.g., tannic acid, carboxymethyl cellulose, polylactic, polyglycolic, or copolymers of polylactic-glycolic acids).

A therapeutically effective amount of a peptide of this invention and a pharmaceutically acceptable carrier substance (e.g., magnesium carbonate, lactose, or a phospholipid with which the therapeutic compound can form a micelle) together form a therapeutic composition (e.g., a pill, tablet, capsule, or liquid) for administration (e.g., orally, intravenously, transdermally, pulmonarily, vaginally, subcutaneously, nasally, iontophoretically, or by intratracheally) to a subject. The pill, tablet or capsule that is to be administered orally can be coated with a substance for protecting the active composition

from the gastric acid or intestinal enzymes in the stomach for a period of time sufficient to allow it to pass undigested into the small intestine. The therapeutic composition can also be in the form of a biodegradable or nonbiodegradable sustained release formulation for subcutaneous or intramuscular administration. See, e.g., U.S. Patents 3,773,919 and 4,767,628 and PCT Application No. WO 94/15587. Continuous administration can also be achieved using an implantable or external pump (e.g., INFUSAID™ pump). The administration can also be conducted intermittently, e.g., single daily injection, or continuously at a low dose, e.g., sustained release formulation.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

Further, a compound of this invention can be administered in a sustained release composition such as those described in the following patents. U.S. Patent No. 5,672,659 teaches sustained release compositions comprising a bioactive agent and a polyester. U.S. Patent No. 5,595,760 teaches sustained release compositions comprising a bioactive agent in a gelable form. U.S. Application No. 08/929,363 filed September 9, 1997, teaches

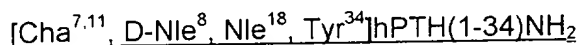
polymeric sustained release compositions comprising a bioactive agent and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising a bioactive agent and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbable sustained release compositions of a bioactive agent. The teachings of the foregoing patents and applications are incorporated herein by reference.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 10 mg/kg of body weight daily are administered.

A preferred dosage range is 0.001 to 0.5 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

The compounds of the instant invention are illustrated by the following examples, but are not limited to the details thereof.

#### EXAMPLE 1



The peptide  $[\text{Cha}^{7,11}, \text{D-Nle}^8, \text{Nle}^{18}, \text{Tyr}^{34}] \text{hPTH}(1-34)\text{NH}_2$  was synthesized on an Applied Biosystems (Foster City, CA) model 430A peptide synthesizer which was modified to do accelerated Boc-chemistry solid phase peptide synthesis. See Schnoize, et al, Int J. Peptide Protein Res., 90:180 (1992). 4-Methylbenzhydrylamine (MBHA) resin (Peninsula, Belmont, CA) with the substitution of 0.93 mmol/g was used. The Boc amino acids (Bachem, CA, Torrance, CA; Nova Biochem., LaJolla, CA) were used with the following side chain protection: Boc-Asn(Xanthyl), Boc-Arg(Tos)-OH, Boc-Asp(OcHex)-OH, Boc-Glu(OcHex)-OH, Boc-His(DNP)-OH, Boc-Cha-OH, Boc-D-Nle-OH, Boc-Nle-OH, Boc-Val-OH, Boc-Leu-OH, Boc-Gly-OH, Boc-Gln-OH, Boc-Ile-OH, Boc-Lys(2CIZ)-OH, Boc-Ser(Bzl)-OH; Boc-Trp(formyl)-OH and Boc-Tyr(Br-Z)-OH (where Z is benzyloxycarbonyl). The synthesis was carried out on a 0.14 mmol scale. The Boc groups were removed by treatment with 100% TFA for 2 x 1 min. Boc amino acids (2.5 mmol) were pre-activated with HBTU (2.0 mmol) and DIEA (1.0 mL) in 4 mL of DMF and were coupled without prior neutralization of the peptide-resin TFA salt. Coupling times were about 5 min.

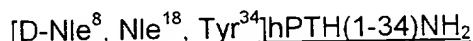
At the end of the assembly of the peptide chain, the resin was treated with a solution of 20% mercaptoethanol/10% DIEA in DMF for 2 x 30 min. to remove the DNP group on the



His side chain. The resin was washed with DMF. The N-terminal Boc group was then removed by treatment with 100% TFA for 2 x 2 min. The resin was washed with DMF and was treated with ethanolamine:H<sub>2</sub>O:DMF/15:15:70 for 2 x 30 min. to remove the formyl protecting group on Trp residue. The partially-deprotected peptide-resin was washed with DMF and DCM and dried *in vacuo*. The final cleavage was done by stirring the peptide-resin in 10 mL of HF containing 1 mL of anisole and dithiothreitol (24 mg) at about 0°C for about 75 min. HF was removed by a flow of nitrogen. The residue was washed with ether (6 x 10 mL) and extracted with 4N HOAc (6 x 10 mL).

The peptide mixture in the aqueous extract was purified on a reverse-phase preparative high pressure liquid chromatography (HPLC) using a reverse phase VYDAC<sup>TM</sup> C<sub>18</sub> column (Nest Group, Southborough, MA). The column was eluted with a linear gradient (10% to 45% of solution B in solution A over 130 min.) at a flow rate of 10 mL/min (Solution A = water containing 0.1% TFA; Solution B = acetonitrile containing 0.1% of TFA). Fractions were collected and checked on analytical HPLC. Those containing pure product were combined and lyophilized to dryness. 114 mg of a white solid was obtained. Purity was >98% based on analytical HPLC analysis. Electro-spray mass spectrometer analysis gave the molecular weight at 4176.4 (in agreement with the calculated molecular weight of 4176.9).

## EXAMPLE 2



Boc-protected amino acids, N-hydroxybenzotriazole (HOBt), N,N'-dicyclohexylcarbodiimide (DCC) and *p*-methylbenzhydrylamine resin were purchased from Applied Biosystems (Foster City, CA). Boc-(3-Iodo)Tyrosine[O-(3-BrBz)] was purchased from Peninsula Laboratories (Belmont, CA). B&J brand dichloromethane. N-methylpyrrolidone (NMP) and acetonitrile were obtained from Baxter (McGraw Park, IL). All other reagents are commercially available, for example from Sigma (St. Louis, MO). The title peptide was synthesized by solid-phase Boc/HOBt/NMP chemistry on an automated Applied Biosystems 430A peptide synthesizer using software version 1.40. The following side-chain protected N- $\alpha$ -Boc-amino derivatives were used in the course of the automated solid-phase peptide synthesis: Arg(N<sup>G</sup>-tosyl), Asp(O-cHex), Glu(O-Bzl), His(N<sup>n</sup>-Bom), Lys(N<sup>ε</sup>-2-CI-Z), Ser(O-Bzl), Thr(O-Bzl), and Tyr(2-Br-Z). Synthesis started at a 0.5 mmol scale and was split into two halves after the incorporation of Glu<sup>22</sup>. The following residues were incorporated by double coupling cycles: Arg<sup>25</sup>, Leu<sup>24</sup>, Val<sup>21</sup>, Arg<sup>20</sup>, Glu<sup>19</sup>, Leu<sup>15</sup>, His<sup>14</sup>,

Lys<sup>13</sup>, His<sup>9</sup>, Phe<sup>7</sup>, Gln<sup>6</sup> and Ile<sup>5</sup>. The Nle in positions 18 and 8 was introduced in the form of pre-dissolved NMP solution and the Activator cycle was modified accordingly. Cleavage of the peptide from the  $\rho$ MBHA resin utilized liquid hydrogen fluoride and followed the "Low-High" procedure. The "Low-HF" step included mixing the suspension of the resin-bound peptide in a mixture (20 mL/g of resin-bound peptide) containing (% vol) 60% dimethylsulfide, 5%  $\rho$ -thiocresol, 5%  $\rho$ -cresol, 5% ethane dithiol, and 25% HF for about 2 hours at about 0°C. After removal of the volatile reagent under vacuum and washing the resin-bound peptide consecutively with petroleum-ether and ether it was returned to the reaction vessel for the "High-HF" step. The resin-bound peptide was resuspended in a mixture (20 mL/g of resin-bound peptide) containing (% vol) 5% butane dithiol, 5%  $\rho$ -cresol, and 90% HF for about 1 hour at about 0°C. After removing the reagents as previously described the crude peptide was dissolved in 50% (v/v) acetic acid and the solution was diluted with water and lyophilized. The peptide was purified by preparative reverse-phase high performance liquid chromatography (RP-HPLC) (PrepPak VYDAC® C18, 300Å cartridge, 15  $\mu$ m, 5.5x35 cm). The solvent system employed included a two solvent system: A: 0.1% (v/v) TFA in water and B: 0.1% (v/v) TFA in acetonitrile, generating the following linear gradient: 0-15% B in A in the first 10 min followed by 15-45% B in A in the next 120 min at a flow-rate of 70 mL/min and monitored at 220 nm. Fractions were analyzed on an analytical RP-HPLC system (VYDAC® (C18, 300Å, 5  $\mu$ m, 4.6x150cm) employing a linear gradient of 20-50% B in A for 30 min at a flow rate of 1 ml/min and monitored at 220 nm, the retention time is 18.24 minutes. The pure fractions were pooled and the acetonitrile removed under vacuum. The residual was lyophilized to yield a white powder. Purity and structure of the peptides were confirmed by analytical RP-HPLC, amino acid analysis, and Fast Atom Bombardment Mass Spectrometry, mass spec. = 4097.0.

### EXAMPLES 3-5

Examples 3-4 were synthesized substantially according to the procedure of Example 1 using the appropriate, protected amino acids and Example 5 was synthesized substantially according to Example 2 using the appropriate, protected amino acids.

| Example | Name   | Mass Spec. |
|---------|--|------------|
| 3       | [Cha <sup>7,11</sup> , des-Met <sup>8</sup> , Nle <sup>18</sup> , Tyr <sup>34</sup> ]hPTH(1-34)NH <sub>2</sub>   | 4063.5     |
| 4       | [Cha <sup>7,11</sup> , D-Nle <sup>8</sup> , des-Met <sup>18</sup> , Tyr <sup>34</sup> ]hPTH(1-34)NH <sub>2</sub> | 4063.4     |
| 5       | [D-Bpa <sup>8</sup> Tyr <sup>34</sup> ]hPTH-(1-34)NH <sub>2</sub>  | 4320.7     |

### EXAMPLES 6-86

Examples 6 to 86 can be synthesized substantially according to the procedure of Example 1 using the appropriate, protected amino acids.

- 5 Example 6: [D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 7: [D-Nle<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 8: [D-Leu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 9: [D-Cha<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 10: [D-Phe<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
10 Example 11: [D-Nal<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 12: [D-Abu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 13: [D-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 14: [Cha<sup>7,11</sup>, D-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 15: [D-Ile<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
15 Example 16: [Cha<sup>7,11</sup>, D-Ile<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 17: [D-Ile<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 18: [D-Leu<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 19: [Cha<sup>7,11</sup>, D-Leu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 20: [D-Val<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
20 Example 21: [Cha<sup>7,11</sup>, D-Val<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 22: [D-Val<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 23: [D-Cha<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 24: [Cha<sup>7,11</sup>, D-Cha<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 25: [D-Ala<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
25 Example 26: [Cha<sup>7,11</sup>, D-Ala<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 27: [D-Ala<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 28: [D-Phe<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 29: [Cha<sup>7,11</sup>, D-Phe<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 30: [D-Met<sup>8</sup>]hPTH(7-34)NH<sub>2</sub>  
30 Example 31: [D-Nal<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 32: [D-Trp<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 33: [Cha<sup>7,11</sup>, D-Trp<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>  
Example 34: [D-Trp<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

- Example 35: [D-Abu<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 36: [Cha<sup>7,11</sup>, D-Abu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 37: [des-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 38: [Cha<sup>7,11</sup>, des-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>
- 5 Example 39: [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 40: [des-Met<sup>8</sup>, des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 41: [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 42: [des-Met<sup>8</sup>, Nle<sup>13</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 43: [des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub>
- 10 Example 44: [Cha<sup>7,11</sup>, des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 45: [Cha<sup>7,11</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 46: [D-Nle<sup>8</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 47: [des-Glu<sup>6</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 48: [des-Leu<sup>7</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- 15 Example 49: [des-His<sup>9</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 50: [des-Asn<sup>10</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 51: [des-Leu<sup>11</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 52: [des-Gly<sup>12</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 53: [des-Lys<sup>13</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- 20 Example 54: [des-His<sup>14</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 55: [des-Leu<sup>15</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 56: [des-Asn<sup>16</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 57: [des-Ser<sup>17</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 58: [des-Glu<sup>19</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- 25 Example 59: [des-Arg<sup>20</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 60: [des-Val<sup>21</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 61: [des-Glu<sup>22</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 62: [des-Glu<sup>6</sup>, Cha<sup>7,11</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 63: [des-Leu<sup>7</sup>, Nle<sup>8,18</sup>, Cha<sup>11</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- 30 Example 64: [Cha<sup>7,11</sup>, des-His<sup>9</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 65: [des-Glu<sup>6</sup>, Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 66: [des-Leu<sup>7</sup>, D-Nle<sup>8</sup>, Cha<sup>11</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>
- Example 67: [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, des-His<sup>9</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 68: [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, des-His<sup>9</sup>, des-Asn<sup>10</sup>]hPTH(1-34)NH<sub>2</sub>

Example 69: [Cha<sup>7,11</sup>, des-Ser<sup>17</sup>, des-Met<sup>18</sup>, des-Glu<sup>19</sup>]hPTH(1-34)NH<sub>2</sub>

Example 70: [D-Met<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

Example 71: [D-Met<sup>8</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>

5 Example 72: [D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(7-34)NH<sub>2</sub>

Example 73: [D-Nle<sup>8</sup>, Nle<sup>18</sup>]hPTH(7-34)NH<sub>2</sub>

Example 74: [Ile<sup>5</sup>, D-Leu<sup>8</sup>]hPTHrP(1-34)NH<sub>2</sub>

Example 75: [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>

Example 76: [Ile<sup>5</sup>, des-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>

10 Example 77: [Ile<sup>5</sup>, des-Leu<sup>8</sup>]hPTHrP(1-34)NH<sub>2</sub>

Example 78: [des-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>

Example 79: [Ile<sup>5</sup>, des-Leu<sup>18</sup>]hPTHrP(1-34)NH<sub>2</sub>

Example 80: [Ile<sup>5</sup>, des-Leu<sup>18</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>

Example 81: [des-Leu<sup>18</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>

15 Example 82: [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25</sup>, Leu<sup>23,28,31</sup>, Lys<sup>26,30</sup>, Aib<sup>29</sup>]hPTHrP(1-34)NH<sub>2</sub>

Example 83: [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25</sup>, Trp<sup>23</sup>, Lys<sup>26,30</sup>, Leu<sup>28,31</sup>, Aib<sup>29</sup>]hPTHrP(1-34)NH<sub>2</sub>

Example 84: [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25,29</sup>, Leu<sup>23,28,31</sup>, Lys<sup>26,30</sup>]hPTHrP(1-34)NH<sub>2</sub>

Example 85: [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25,29</sup>, Trp<sup>23</sup>, Lys<sup>26,30</sup>, Leu<sup>28,31</sup>]hPTHrP(1-34)NH<sub>2</sub>

Example 86: [D-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(7-34)NH<sub>2</sub>

20

## CLAIMS

What is claimed is:

1. A PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof that selectively binds to the PTH2 receptor.

5 2. A PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof according to claim 1 where said analogue is a selective PTH2 receptor agonist.

3. A PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof according to claim 1 where said analogue is a selective PTH2  
10 receptor antagonist.

4. A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 1 or a pharmaceutically-acceptable salt thereof.

5. A method of selectively eliciting an agonist response from the PTH2 receptor  
15 which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 2 or a pharmaceutically acceptable salt thereof.

6. A method of selectively eliciting an antagonist response from the PTH2 receptor which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 3 or a pharmaceutically acceptable salt thereof.

20 7. An analogue according to claim 1 wherein said analogue is of formula (I),  
(R<sup>1</sup>R<sup>2</sup>)-A<sup>1</sup>-A<sup>2</sup>-A<sup>3</sup>-A<sup>4</sup>-A<sup>5</sup>-A<sup>6</sup>-A<sup>7</sup>-A<sup>8</sup>-A<sup>9</sup>-A<sup>10</sup>-A<sup>11</sup>-A<sup>12</sup>-A<sup>13</sup>-A<sup>14</sup>-A<sup>15</sup>-A<sup>16</sup>-A<sup>17</sup>-A<sup>18</sup>-A<sup>19</sup>-A<sup>20</sup>-A<sup>21</sup>-A<sup>22</sup>-A<sup>23</sup>-A<sup>24</sup>-  
A<sup>25</sup>-A<sup>26</sup>-A<sup>27</sup>-A<sup>28</sup>-A<sup>29</sup>-A<sup>30</sup>-A<sup>31</sup>-A<sup>32</sup>-A<sup>33</sup>-A<sup>34</sup>-A<sup>35</sup>-A<sup>36</sup>-A<sup>37</sup>-A<sup>38</sup>-R<sup>3</sup>,

(I)

or a pharmaceutically-acceptable salt thereof wherein

25 A<sup>1</sup> is a hydrophilic or a lipophilic amino acid;

A<sup>2</sup> is a lipophilic amino acid;

A<sup>3</sup> is a hydrophilic or a lipophilic amino acid;

A<sup>4</sup> is a hydrophilic amino acid

A<sup>5</sup> is a hydrophilic or a lipophilic amino acid;

30 A<sup>6</sup> is a hydrophilic amino acid or is deleted;

A<sup>7</sup> is a hydrophilic or a lipophilic amino acid or is deleted;

A<sup>8</sup> is a lipophilic amino acid or is deleted;

A<sup>9</sup> is a hydrophilic amino acid or is deleted;

- A<sup>10</sup> is a hydrophilic amino acid or is deleted;  
A<sup>11</sup> is a hydrophilic or a lipophilic amino acid or is deleted;  
A<sup>12</sup> is a hydrophilic or a lipophilic amino acid or is deleted;  
A<sup>13</sup> is a hydrophilic amino acid;  
5 A<sup>14</sup> is a hydrophilic amino acid or is deleted;  
A<sup>15</sup> is a lipophilic amino acid or is deleted;  
A<sup>16</sup> is a hydrophilic or a lipophilic amino acid or is deleted;  
A<sup>17</sup> is a hydrophilic or a lipophilic amino acid or is deleted;  
A<sup>18</sup> is a lipophilic amino acid or is deleted;  
10 A<sup>19</sup> is a hydrophilic or a lipophilic amino acid or is deleted;  
A<sup>20</sup> is a hydrophilic amino acid or is deleted;  
A<sup>21</sup> is a hydrophilic or a lipophilic amino acid or is deleted;  
A<sup>22</sup> is a lipophilic or a hydrophilic amino acid or is deleted;  
A<sup>23</sup> is a hydrophilic or a lipophilic amino acid;  
15 A<sup>24</sup> is a hydrophilic or a lipophilic amino acid;  
A<sup>25</sup> is a hydrophilic amino acid;  
A<sup>26</sup> is a hydrophilic amino acid;  
A<sup>27</sup> is a lipophilic or a hydrophilic amino acid;  
A<sup>28</sup> is a lipophilic amino acid;  
20 A<sup>29</sup> is a lipophilic or a hydrophilic amino acid;  
A<sup>30</sup> is a hydrophilic or a lipophilic amino acid;  
A<sup>31</sup> is a lipophilic or a hydrophilic amino acid or is deleted;  
A<sup>32</sup> is a hydrophilic amino acid or is deleted;  
A<sup>33</sup> is a hydrophilic amino acid or is deleted;  
25 A<sup>34</sup> is a lipophilic amino acid or is deleted;  
A<sup>35</sup> is a lipophilic amino acid or is deleted;  
A<sup>36</sup> is a lipophilic or a hydrophilic amino acid or is deleted;  
A<sup>37</sup> is a lipophilic amino acid or is deleted;  
A<sup>38</sup> is a lipophilic or a hydrophilic amino acid or is deleted;  
30 R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl-(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl,

or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl; and

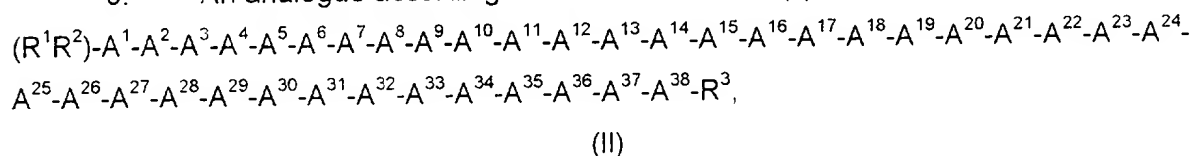
R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1-30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1-30</sub>) hydrocarbon moiety

and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

provided that the compound is not PTH(1-34)R<sup>3</sup>, PTH(1-35)R<sup>3</sup>, PTH(1-36)R<sup>3</sup>, PTH(1-37)R<sup>3</sup>, or PTH(1-38)R<sup>3</sup>.

8. A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 7 or a pharmaceutically-acceptable salt thereof.

9. An analogue according to claim 1 of formula (II),



or a pharmaceutically-acceptable salt thereof wherein

A<sup>1</sup> is Ser, Ala, Dap, Thr, Aib or is deleted;

A<sup>2</sup> is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;

A<sup>3</sup> is Ser, Thr, Aib or is deleted;

A<sup>4</sup> is Glu, Asp or is deleted;

A<sup>5</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;

A<sup>6</sup> is Gln, a hydrophilic amino acid or is deleted;

A<sup>7</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;

A<sup>8</sup> is Met, Nva, Leu, Val, Ile, Cha, Acc, Nle, p-X-Phe, Phe, β-Nal, Bpa, a lipophilic amino acid or is deleted;

A<sup>9</sup> is His, a hydrophilic amino acid or is deleted;

A<sup>10</sup> is Asn, a hydrophilic amino acid or is deleted;

A<sup>11</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a hydrophilic amino acid or is deleted;

A<sup>12</sup> is Gly, Acc, Aib, or is deleted;

A<sup>13</sup> is Lys, Arg or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);

A<sup>14</sup> is His or is deleted;



A<sup>15</sup> is Leu, Val, Nle, Ile, Cha,  $\beta$ -Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;

A<sup>16</sup> is Ser, Asn, Ala, Aib or is deleted;

A<sup>17</sup> is Ser, Thr, Aib or is deleted;

A<sup>18</sup> is Met, Nva, Leu, Val, Ile, Nle, p-X-Phe, Phe,  $\beta$ -Nal, Acc, Cha, Aib or is deleted;

5 A<sup>19</sup> is Glu, Aib or is deleted;

A<sup>20</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>21</sup> is Val, Leu, Ile, Phe, Nle,  $\beta$ -Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;

A<sup>22</sup> is Acc, Aib, Glu or is deleted;

A<sup>23</sup> is Trp, Acc, Phe, p-X-Phe, Aib,  $\beta$ -Nal or Cha;

10 A<sup>24</sup> is Leu, Acc, Ile, Val, Phe,  $\beta$ -Nal, Nle, Aib, p-X-Phe or Cha;

A<sup>25</sup> is Arg, Lys or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);

A<sup>26</sup> is Arg, Lys or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);

A<sup>27</sup> is Lys, Aib, Leu, hArg, Gln, Acc, Arg, Cha, Nle, Ile, Val, Phe,  $\beta$ -Nal, or p-X-Phe, where the Lys is optionally substituted on the  $\epsilon$ -amino group by an acyl group;

15 A<sup>28</sup> is Leu, Acc, Cha, Ile, Val, Phe, Nle,  $\beta$ -Nal, Aib or p-X-Phe;

A<sup>29</sup> is Gln, Acc or Aib;

A<sup>30</sup> is Asp, Lys, Arg or is deleted;

A<sup>31</sup> is Val, Leu, Nle, Acc, Cha, Phe, Ile,  $\beta$ -Nal, Aib, p-X-Phe or is deleted;

A<sup>32</sup> is His or is deleted;

20 A<sup>33</sup> is Asn or is deleted;

A<sup>34</sup> is Phe, Tyr, Amp, Aib,  $\beta$ -Nal, Cha, Nle, Leu, Ile, Acc, p-X-Phe or is deleted;

A<sup>35</sup> is Val, Leu, Nle, Acc, Cha, Phe, Ile,  $\beta$ -Nal, Aib, p-X-Phe or is deleted;

A<sup>36</sup> is Ala, Val, Aib, Acc, Nva, Abu or is deleted;

A<sup>37</sup> is Leu, Val, Nle, Ile, Cha,  $\beta$ -Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or

25 is deleted;

A<sup>38</sup> is Gly, Acc, Aib, or is deleted;

where X for each occurrence is independently selected from the group consisting of OH, a halo and CH<sub>3</sub>;

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl-(C<sub>1-30</sub>)alkyl, naphthyl-(C<sub>1-30</sub>)alkyl, hydroxy-(C<sub>1-30</sub>)alkyl, hydroxy-(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl-(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl-(C<sub>1-30</sub>)alkyl;

30

or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

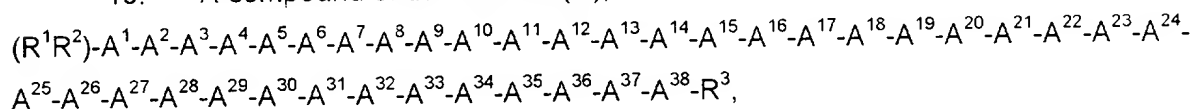
R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1-30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1-30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

n for each occurrence is independently an integer from 1 to 5; and

R<sup>4</sup> for each occurrence is independently (C<sub>1-C30</sub>)alkyl, (C<sub>1-C30</sub>)acyl or -C((NH)(NH<sub>2</sub>));

provided that the compound is not PTH(1-34)R<sup>3</sup>, PTH(1-35)R<sup>3</sup>, PTH(1-36)R<sup>3</sup>, PTH(1-37)R<sup>3</sup>, or PTH(1-38)R<sup>3</sup>.

10. A compound of the formula (III),



(III)

or a pharmaceutically-acceptable salt thereof wherein

A<sup>1</sup> is Ser, Ala, Dap, Thr, Aib or is deleted;

A<sup>2</sup> is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;

A<sup>3</sup> is Ser, Thr, Aib or is deleted;

A<sup>4</sup> is Glu, Asp or is deleted;

A<sup>5</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;

A<sup>6</sup> is Gln, a hydrophilic amino acid or is deleted;

A<sup>7</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or is deleted;

A<sup>8</sup> is Met, Nva, Leu, Val, Ile, Cha, Acc, Nle, p-X-Phe, Phe, β-Nal, Bpa, a lipophilic amino acid or is deleted;

A<sup>9</sup> is His, a hydrophilic amino acid or is deleted;

A<sup>10</sup> is Asn, a hydrophilic amino acid or is deleted;

A<sup>11</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a hydrophilic amino acid or is deleted;

A<sup>12</sup> is Gly, Acc, Aib, or is deleted;

A<sup>13</sup> is Lys, Arg or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);

A<sup>14</sup> is His or is deleted;

A<sup>15</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe or is deleted;

- A<sup>16</sup> is Ser, Asn, Ala, Aib or is deleted;  
A<sup>17</sup> is Ser, Thr, Aib or is deleted;  
A<sup>18</sup> is Met, Nva, Leu, Val, Ile, Nle, p-X-Phe, Phe, β-Nal, Acc, Cha, Aib or is deleted;  
A<sup>19</sup> is Glu, Aib or is deleted;  
5 A<sup>20</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;  
A<sup>21</sup> is Val, Leu, Ile, Phe, Nle, β-Nal, Aib, p-X-Phe, Acc, Cha, Met or is deleted;  
A<sup>22</sup> is Acc, Aib, Glu or is deleted;  
A<sup>23</sup> is Trp, Acc, Phe, p-X-Phe, Aib, β-Nal or Cha;  
A<sup>24</sup> is Leu, Acc, Ile, Val, Phe, β-Nal, Nle, Aib, p-X-Phe or Cha;  
10 A<sup>25</sup> is Arg, Lys or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);  
A<sup>26</sup> is Arg, Lys or HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O);  
A<sup>27</sup> is Lys, Aib, Leu, hArg, Gln, Acc, Arg, Cha, Nle, Ile, Val, Phe, β-Nal, or p-X-Phe, where  
the Lys is optionally substituted on the ε-amino group by an acyl group;  
A<sup>28</sup> is Leu, Acc, Cha, Ile, Val, Phe, Nle, β-Nal, Aib or p-X-Phe;  
15 A<sup>29</sup> is Gln, Acc or Aib;  
A<sup>30</sup> is Asp, Lys, Arg or is deleted;  
A<sup>31</sup> is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal, Aib, p-X-Phe or is deleted;  
A<sup>32</sup> is His or is deleted;  
A<sup>33</sup> is Asn or is deleted;  
20 A<sup>34</sup> is Phe, Tyr, Amp, Aib, β-Nal, Cha, Nle, Leu, Ile, Acc, p-X-Phe or is deleted;  
A<sup>35</sup> is Val, Leu, Nle, Acc, Cha, Phe, Ile, β-Nal, Aib, p-X-Phe or is deleted;  
A<sup>36</sup> is Ala, Val, Aib, Acc, Nva, Abu or is deleted;  
A<sup>37</sup> is Leu, Val, Nle, Ile, Cha, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, a lipophilic amino acid, or  
is deleted;  
25 A<sup>38</sup> is Gly, Acc, Aib, or is deleted;  
where X for each occurrence is independently selected from the group consisting of  
OH, a halo and CH<sub>3</sub>;  
R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1</sub>-  
30)alkyl, (C<sub>2</sub>-30)alkenyl, phenyl-(C<sub>1</sub>-30)alkyl, naphthyl(C<sub>1</sub>-30)alkyl, hydroxy(C<sub>1</sub>-30)alkyl,  
hydroxy(C<sub>2</sub>-30)alkenyl, hydroxy-phenyl(C<sub>1</sub>-30)alkyl or hydroxy-naphthyl(C<sub>1</sub>-30)alkyl;

or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1-30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1-30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

n for each occurrence is independently an integer from 1 to 5; and

R<sup>4</sup> for each occurrence is independently (C<sub>1-C30</sub>)alkyl, (C<sub>1-C30</sub>)acyl or -C((NH)(NH<sub>2</sub>));

provided that when A<sup>8</sup> is not a lipophilic D-amino acid or is not deleted then at least one of A<sup>6</sup>, A<sup>7</sup>, A<sup>9</sup>, A<sup>10</sup>, A<sup>11</sup> and A<sup>12</sup> is a D-amino acid or at least one of A<sup>6</sup>, A<sup>7</sup>, A<sup>9</sup>, A<sup>10</sup>, A<sup>11</sup>, A<sup>12</sup>, A<sup>13</sup>.

10 A<sup>14</sup>, A<sup>15</sup>, A<sup>16</sup>, A<sup>17</sup>, A<sup>18</sup>, A<sup>19</sup>, A<sup>20</sup>, A<sup>21</sup> and A<sup>22</sup> is deleted;

and further provided that when the compound contains a D-amino acid then A<sup>36</sup> is deleted

11. A compound according to claim 10 wherein said compound is

[D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

[D-Nle<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>.

15 [D-Leu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

[D-Cha<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

[D-Phe<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

[D-Nal<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

[D-Abu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

20 [D-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,

[Cha<sup>7,11</sup>, D-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,

[D-Ile<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,

[Cha<sup>7,11</sup>, D-Ile<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

[D-Ile<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

25 [D-Leu<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,

[Cha<sup>7,11</sup>, D-Leu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

[D-Val<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,

[Cha<sup>7,11</sup>, D-Val<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

[D-Val<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

30 [D-Cha<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>.

[Cha<sup>7,11</sup>, D-Cha<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

[D-Ala<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,

[Cha<sup>7,11</sup>, D-Ala<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

- [D-Ala<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [D-Phe<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, D-Phe<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [D-Nal<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,  
 5 [D-Trp<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, D-Trp<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [D-Trp<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [D-Abu<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, D-Abu<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 10 [D-Nle<sup>8</sup>, Nle<sup>18</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, des-Met<sup>8</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Met<sup>8</sup>, des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub>,  
 15 [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Met<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, des-Met<sup>18</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 20 [D-Nle<sup>8</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Glu<sup>6</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Leu<sup>7</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-His<sup>9</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Asn<sup>10</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 25 [des-Leu<sup>11</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Gly<sup>12</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Lys<sup>13</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-His<sup>14</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Leu<sup>15</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 30 [des-Asn<sup>16</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Ser<sup>17</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Glu<sup>19</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Arg<sup>20</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,

- [des-Val<sup>21</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Glu<sup>22</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Glu<sup>6</sup>, Cha<sup>7,11</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Leu<sup>7</sup>, Nle<sup>8,18</sup>, Cha<sup>11</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 5 [Cha<sup>7,11</sup>, des-His<sup>9</sup>, Nle<sup>8,18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Glu<sup>6</sup>, Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [des-Leu<sup>7</sup>, D-Nle<sup>8</sup>, Cha<sup>11</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, des-His<sup>9</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-31)NH<sub>2</sub>,  
 10 [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, des-His<sup>9</sup>, des-Asn<sup>10</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, des-Ser<sup>17</sup>, des-Met<sup>18</sup>, des-Glu<sup>19</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [D-Met<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 15 [D-Met<sup>8</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [D-Bpa<sup>8</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>,  
 [D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(7-34)NH<sub>2</sub>,  
 [D-Nle<sup>8</sup>, Nle<sup>18</sup>]hPTH(7-34)NH<sub>2</sub> or  
 [D-Met<sup>8</sup>]hPTH(7-34)NH<sub>2</sub>.  
 20 12. A compound according to claim 11 wherein said compound is  
 [Cha<sup>7,11</sup>, des-Met<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH-(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, des-Met<sup>18</sup>, Tyr<sup>34</sup>]hPTH-(1-34)NH<sub>2</sub>,  
 [Cha<sup>7,11</sup>, D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH-(1-34)NH<sub>2</sub>,  
 [D-Nle<sup>8</sup>, Nle<sup>18</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub> or [D-Bpa<sup>8</sup>, Tyr<sup>34</sup>]hPTH(1-34)NH<sub>2</sub>.  
 25 13. A PTHrP analogue of formula (IV) that selectively binds to the PTH2  
 receptor,  
 (R<sup>1</sup>R<sup>2</sup>)-A<sup>1</sup>-A<sup>2</sup>-A<sup>3</sup>-A<sup>4</sup>-A<sup>5</sup>-A<sup>6</sup>-A<sup>7</sup>-A<sup>8</sup>-A<sup>9</sup>-A<sup>10</sup>-A<sup>11</sup>-A<sup>12</sup>-A<sup>13</sup>-A<sup>14</sup>-A<sup>15</sup>-A<sup>16</sup>-A<sup>17</sup>-A<sup>18</sup>-A<sup>19</sup>-A<sup>20</sup>-A<sup>21</sup>-A<sup>22</sup>-A<sup>23</sup>-A<sup>24</sup>-  
 A<sup>25</sup>-A<sup>26</sup>-A<sup>27</sup>-A<sup>28</sup>-A<sup>29</sup>-A<sup>30</sup>-A<sup>31</sup>-A<sup>32</sup>-A<sup>33</sup>-A<sup>34</sup>-A<sup>35</sup>-A<sup>36</sup>-A<sup>37</sup>-A<sup>38</sup>-R<sup>3</sup>,  
 (IV)  
 30 or a pharmaceutically acceptable salt thereof, wherein  
 A<sup>1</sup> is Ala, Ser, Dap, Thr, Aib or is deleted;  
 A<sup>2</sup> is Val or is deleted;  
 A<sup>3</sup> is Ser, Aib, Thr or is deleted;

A<sup>4</sup> is Glu, Asp or is deleted;

A<sup>5</sup> is His, Ile, Acc, Val, Nle, Phe, Leu, p-X-Phe, β-Nal, Aib, Cha or is deleted;

A<sup>6</sup> is Gln, a hydrophilic amino acid or is deleted;

A<sup>7</sup> is Leu, Val, Cha, Nle, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, Aib, a lipophilic amino acid or is

5 deleted;

A<sup>8</sup> is Leu, Met, Acc, Cha, Aib, Nle, Phe, Ile, Val, β-Nal, p-X-Phe, a lipophilic amino acid or is deleted;

A<sup>9</sup> is His, a hydrophilic amino acid or is deleted;

A<sup>10</sup> is Asp, Asn, a hydrophilic amino acid or is deleted;

10 A<sup>11</sup> is Lys, Arg, Leu, Cha, Aib, p-X-Phe, Ile, Val, Nle, Acc, Phe, β-Nal, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O), a lipophilic D-amino acid, a hydrophilic amino acid or is deleted;

A<sup>12</sup> is Gly, Acc, Aib or is deleted;

A<sup>13</sup> is Lys, Arg, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>14</sup> is Ser, His or is deleted;

15 A<sup>15</sup> is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;

A<sup>16</sup> is Gln, Aib or is deleted;

A<sup>17</sup> is Asp, Aib or is deleted;

A<sup>18</sup> is Leu, Aib, Acc, Cha, Phe, Ile, Nle, β-Nal, Val, p-X-Phe or is deleted;

A<sup>19</sup> is Arg, Lys, Aib, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

20 A<sup>20</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>21</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>22</sup> is Phe, Glu, Aib, Acc, p-X-Phe, β-Nal, Val, Leu, Ile, Nle or Cha;

A<sup>23</sup> is Phe, Leu, Lys, Acc, Cha, β-Nal, Aib, Nle, Ile, p-X-Phe, Val or Trp;

A<sup>24</sup> is Leu, Lys, Acc, Nle, Ile, Val, Phe, β-Nal, Aib, p-X-Phe, Arg or Cha;

25 A<sup>25</sup> is His, Lys, Aib, Acc, Arg or Glu;

A<sup>26</sup> is His, Aib, Acc, Arg or Lys;

A<sup>27</sup> is Leu, Lys, Acc, Arg, Ile, Val, Phe, Aib, Nle, β-Nal, p-X-Phe or Cha;

A<sup>28</sup> is Ile, Leu, Lys, Acc, Cha, Val, Phe, p-X-Phe, Nle, β-Nal, Aib or is deleted;

A<sup>29</sup> is Ala, Glu, Acc, Aib or is deleted;

30 A<sup>30</sup> is Glu, Leu, Nle, Cha, Aib, Acc, Lys, Arg or is deleted;

A<sup>31</sup> is Ile, Leu, Cha, Lys, Acc, Phe, Val, Nle, β-Nal, Arg or is deleted;

A<sup>32</sup> is His or is deleted;

A<sup>33</sup> is Thr, Ser or is deleted;

A<sup>34</sup> is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;

A<sup>35</sup> is Glu, Asp or is deleted;

A<sup>36</sup> is Ile, Acc, Cha, Leu, Phe, Nle, β-Nal, Trp, p-X-Phe, Val, Aib or is deleted;

5 A<sup>37</sup> is Arg, Lys, HN-CH((CH<sub>2</sub>)<sub>n</sub>NH-R<sup>4</sup>)-C(O) or is deleted;

A<sup>38</sup> is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl-(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl

10 or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1-30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1-30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

15 n for each occurrence is independently an integer from 1 to 5; and

R<sup>4</sup> for each occurrence is independently (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>1</sub>-C<sub>30</sub>)acyl or -C((NH)(NH<sub>2</sub>)); provided that the compound is not PTHrP(1-34)R<sup>3</sup>, PTHrP(1-35)R<sup>3</sup>, PTHrP(1-36)R<sup>3</sup>, PTHrP(1-37)R<sup>3</sup> or PTHrP(1-38)R<sup>3</sup>,

20 and further provided that the compound is not [Ile<sup>5</sup>, Trp<sup>23</sup>]PTHrP(1-36) or [Trp<sup>23</sup>]PTHrP(1-36).

14. A compound of formula (V),

(R<sup>1</sup>R<sup>2</sup>)-A<sup>1</sup>-A<sup>2</sup>-A<sup>3</sup>-A<sup>4</sup>-A<sup>5</sup>-A<sup>6</sup>-A<sup>7</sup>-A<sup>8</sup>-A<sup>9</sup>-A<sup>10</sup>-A<sup>11</sup>-A<sup>12</sup>-A<sup>13</sup>-A<sup>14</sup>-A<sup>15</sup>-A<sup>16</sup>-A<sup>17</sup>-A<sup>18</sup>-A<sup>19</sup>-A<sup>20</sup>-A<sup>21</sup>-A<sup>22</sup>-A<sup>23</sup>-A<sup>24</sup>-A<sup>25</sup>-A<sup>26</sup>-A<sup>27</sup>-A<sup>28</sup>-A<sup>29</sup>-A<sup>30</sup>-A<sup>31</sup>-A<sup>32</sup>-A<sup>33</sup>-A<sup>34</sup>-A<sup>35</sup>-A<sup>36</sup>-A<sup>37</sup>-A<sup>38</sup>-R<sup>3</sup>,

(V)

25 or a pharmaceutically acceptable salt thereof, wherein

A<sup>1</sup> is Ala, Ser, Dap, Thr, Aib or is deleted;

A<sup>2</sup> is Val or is deleted;

A<sup>3</sup> is Ser, Aib, Thr or is deleted;

A<sup>4</sup> is Glu, Asp or is deleted;

30 A<sup>5</sup> is His, Ile, Acc, Val, Nle, Phe, Leu, p-X-Phe, β-Nal, Aib, Cha or is deleted;

A<sup>6</sup> is Gln, a hydrophilic amino acid or is deleted;

A<sup>7</sup> is Leu, Val, Cha, Nle, β-Nal, Trp, Pal, Acc, Phe, p-X-Phe, Aib, a lipophilic amino acid or is deleted;



- $A^8$  is Leu, Met, Acc, Cha, Aib, Nle, Phe, Ile, Val,  $\beta$ -Nal, p-X-Phe, a lipophilic amino acid or is deleted;
- $A^9$  is His, a hydrophilic amino acid or is deleted;
- $A^{10}$  is Asp, Asn, a hydrophilic amino acid or is deleted;
- 5  $A^{11}$  is Lys, Arg, Leu, Cha, Aib, p-X-Phe, Ile, Val, Nle, Acc, Phe,  $\beta$ -Nal,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$ , a lipophilic D-amino acid, a hydrophilic amino acid or is deleted;
- $A^{12}$  is Gly, Acc, Aib or is deleted;
- $A^{13}$  is Lys, Arg,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$  or is deleted;
- $A^{14}$  is Ser, His or is deleted;
- 10  $A^{15}$  is Ile, Acc, Cha, Leu, Phe, Nle,  $\beta$ -Nal, Trp, p-X-Phe, Val, Aib or is deleted;
- $A^{16}$  is Gln, Aib or is deleted;
- $A^{17}$  is Asp, Aib or is deleted;
- $A^{18}$  is Leu, Aib, Acc, Cha, Phe, Ile, Nle,  $\beta$ -Nal, Val, p-X-Phe or is deleted;
- $A^{19}$  is Arg, Lys, Aib,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$  or is deleted;
- 15  $A^{20}$  is Arg, Lys,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$  or is deleted;
- $A^{21}$  is Arg, Lys,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$  or is deleted;
- $A^{22}$  is Phe, Glu, Aib, Acc, p-X-Phe,  $\beta$ -Nal, Val, Leu, Ile, Nle or Cha;
- $A^{23}$  is Phe, Leu, Lys, Acc, Cha,  $\beta$ -Nal, Aib, Nle, Ile, p-X-Phe, Val or Trp;
- $A^{24}$  is Leu, Lys, Acc, Nle, Ile, Val, Phe,  $\beta$ -Nal, Aib, p-X-Phe, Arg or Cha;
- 20  $A^{25}$  is His, Lys, Aib, Acc, Arg or Glu;
- $A^{26}$  is His, Aib, Acc, Arg or Lys;
- $A^{27}$  is Leu, Lys, Acc, Arg, Ile, Val, Phe, Aib, Nle,  $\beta$ -Nal, p-X-Phe or Cha;
- $A^{28}$  is Ile, Leu, Lys, Acc, Cha, Val, Phe, p-X-Phe, Nle,  $\beta$ -Nal, Aib or is deleted;
- $A^{29}$  is Ala, Glu, Acc, Aib or is deleted;
- 25  $A^{30}$  is Glu, Leu, Nle, Cha, Aib, Acc, Lys, Arg or is deleted;
- $A^{31}$  is Ile, Leu, Cha, Lys, Acc, Phe, Val, Nle,  $\beta$ -Nal, Arg or is deleted;
- $A^{32}$  is His or is deleted;
- $A^{33}$  is Thr, Ser or is deleted;
- $A^{34}$  is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle,  $\beta$ -Nal, Aib, Acc or is deleted;
- 30  $A^{35}$  is Glu, Asp or is deleted;
- $A^{36}$  is Ile, Acc, Cha, Leu, Phe, Nle,  $\beta$ -Nal, Trp, p-X-Phe, Val, Aib or is deleted;
- $A^{37}$  is Arg, Lys,  $\text{HN-CH}((\text{CH}_2)_n\text{NH-R}^4)\text{-C(O)}$  or is deleted;

A<sup>38</sup> is Ala, Phe, Tyr, Cha, Val, Ile, Leu, Nle, β-Nal, Aib, Acc or is deleted;

R<sup>1</sup> and R<sup>2</sup> are each independently selected from the group consisting of H, (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl-(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

5 or one of R<sup>1</sup> or R<sup>2</sup> is COE<sup>1</sup> where E<sup>1</sup> is (C<sub>1-30</sub>)alkyl, (C<sub>2-30</sub>)alkenyl, phenyl(C<sub>1-30</sub>)alkyl, naphthyl(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>1-30</sub>)alkyl, hydroxy(C<sub>2-30</sub>)alkenyl, hydroxy-phenyl(C<sub>1-30</sub>)alkyl or hydroxy-naphthyl(C<sub>1-30</sub>)alkyl;

R<sup>3</sup> is OH, NH<sub>2</sub>, (C<sub>1-30</sub>)alkoxy or NH-Y-CH<sub>2</sub>-Z, where Y is a (C<sub>1-30</sub>) hydrocarbon moiety and Z is CO<sub>2</sub>H or CONH<sub>2</sub>;

10 n for each occurrence is independently an integer from 1 to 5; and

R<sup>4</sup> for each occurrence is independently (C<sub>1</sub>-C<sub>30</sub>)alkyl, (C<sub>1</sub>-C<sub>30</sub>)acyl or -C((NH)(NH<sub>2</sub>));

provided that when A<sup>8</sup> is not a lipophilic D-amino acid or is not deleted then at least one of A<sup>6</sup>, A<sup>7</sup>, A<sup>9</sup>, A<sup>10</sup>, A<sup>11</sup> and A<sup>12</sup> is a D-amino acid or at least one of A<sup>6</sup>, A<sup>7</sup>, A<sup>9</sup>, A<sup>10</sup>, A<sup>11</sup>, A<sup>12</sup>, A<sup>13</sup>, A<sup>14</sup>, A<sup>15</sup>, A<sup>16</sup>, A<sup>17</sup>, A<sup>18</sup>, A<sup>19</sup>, A<sup>20</sup>, A<sup>21</sup> and A<sup>22</sup> is deleted.

15 15. A compound according to claim 14 wherein said compound is

[Ile<sup>5</sup>, D-Leu<sup>8</sup>]hPTHrP(1-34)NH<sub>2</sub>,

[Ile<sup>5</sup>, D-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>,

[Ile<sup>5</sup>, des-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>,

[Ile<sup>5</sup>, des-Leu<sup>8</sup>]hPTHrP(1-34)NH<sub>2</sub>,

20 [des-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>,

[Ile<sup>5</sup>, des-Leu<sup>18</sup>]hPTHrP(1-34)NH<sub>2</sub>,

[Ile<sup>5</sup>, des-Leu<sup>18</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>,

[des-Leu<sup>18</sup>, Trp<sup>23</sup>]hPTHrP(1-34)NH<sub>2</sub>,

[Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25</sup>, Leu<sup>23,28,31</sup>, Lys<sup>26,30</sup>, Aib<sup>29</sup>]hPTHrP(1-34)NH<sub>2</sub>,

25 [Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25</sup>, Trp<sup>23</sup>, Lys<sup>26,30</sup>, Leu<sup>28,31</sup>, Aib<sup>29</sup>]hPTHrP(1-34)NH<sub>2</sub>,

[Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25,29</sup>, Leu<sup>23,28,31</sup>, Lys<sup>26,30</sup>]hPTHrP(1-34)NH<sub>2</sub>,

[Ile<sup>5</sup>, D-Leu<sup>8</sup>, Glu<sup>22,25,29</sup>, Trp<sup>23</sup>, Lys<sup>26,30</sup>, Leu<sup>28,31</sup>]hPTHrP(1-34)NH<sub>2</sub> or

[D-Leu<sup>8</sup>, Trp<sup>23</sup>]hPTHrP(7-34)NH<sub>2</sub>.

30 16. A method of selectively binding the PTH2 receptor which comprises administering to a patient in need thereof an analogue according to claim 9 or a pharmaceutically acceptable salt thereof.

17. A method of selectively binding the PTH2 receptor which comprises administering to a patient in need thereof a compound according to claim 10 or a pharmaceutically acceptable salt thereof.

18. A method of selectively binding the PTH2 receptor which comprises  
5 administering to a patient in need thereof a compound according to claim 11 or a pharmaceutically acceptable salt thereof.

19. A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof a compound according to claim 12 or a pharmaceutically acceptable salt thereof.

10 20. A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof an analogue according to claim 13 or a pharmaceutically acceptable salt thereof.

21 A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof a compound according to claim 14 or a  
15 pharmaceutically acceptable salt thereof.

22. A method of selectively binding a PTH2 receptor which comprises administering to a patient in need thereof a compound according to claim 15 or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising an analogue according to claim 9  
20 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

24. A pharmaceutical composition comprising a compound according to claim 10 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

25. A pharmaceutical composition comprising a compound according to claim 11 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

25 26. A pharmaceutical composition comprising a compound according to claim 12 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

27. A pharmaceutical composition comprising an analogue according to claim 13 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier

28. A pharmaceutical composition comprising a compound according to claim 14  
30 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

29. A pharmaceutical composition comprising a compound according to claim 15 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

30. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 7, sufficient to inhibit the activation of the PTH2 receptor of said patient.

5 31. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 9, sufficient to inhibit the activation of the PTH2 receptor of said patient.

10 32. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound according to claim 10, sufficient to inhibit the activation of the PTH2 receptor of said patient.

15 33. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound according to claim 11, sufficient to inhibit the activation of the PTH2 receptor of said patient.

20 34. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound according to claim 12, sufficient to inhibit the activation of the PTH2 receptor of said patient.

25 35. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of an analogue according to claim 13, sufficient to inhibit the activation of the PTH2 receptor of said patient.

30 36. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound according to claim 14, sufficient to inhibit the activation of the PTH2 receptor of said patient.

37. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a compound according to claim 15, sufficient to inhibit the activation of the PTH2 receptor of said patient.

38. A method according to claim 30 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

39. A method according to claim 31 wherein said medical disorder is abnormal  
5 CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

40. A method according to claim 32 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

10 41. A method according to claim 33 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

42. A method according to claim 34 wherein said medical disorder is abnormal  
15 CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

43. A method according to claim 35 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

44. A method according to claim 36 wherein said medical disorder is abnormal  
20 CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalamic disease.

45. A method according to claim 37 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalmic disease.

25 46. A method of treating a medical disorder that results from altered or excessive action of the PTH2 receptor, which comprises administering to a patient in need thereof an effective amount of a PTH analogue or a truncated PTH analogue or a pharmaceutically acceptable salt thereof according to claim 1, sufficient to inhibit the activation of the PTH2 receptor of said patient.

30 47. A method according to claim 46 wherein said medical disorder is abnormal CNS functions, abnormal pancreatic functions, divergence from normal mineral metabolism and homeostasis, male infertility, abnormal blood pressure or a hypothalmic disease.

**ABSTRACT**

This invention relates to a series of PTH and PTHrP analogues that selectively bind to PTH2 receptors and as such may be useful in treating abnormal CNS functions; abnormal pancreatic functions; divergence from normal mineral metabolism and homeostasis, male infertility, regulation of abnormal blood pressure; and hypothalamic disease.

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Docket No.

BPC073

# Declaration and Power of Attorney For Patent Application

## English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**PTH2 Receptor Selective Compounds**

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on \_\_\_\_\_ as United States Application No. or PCT International Application Number \_\_\_\_\_ and was amended on \_\_\_\_\_ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

\_\_\_\_\_  
(Number)

\_\_\_\_\_  
(Country)

\_\_\_\_\_  
(Day/Month/Year Filed)

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\_\_\_\_\_  
(Number)

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(Country)

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(Day/Month/Year Filed)

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\_\_\_\_\_  
(Number)

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(Country)

\_\_\_\_\_  
(Day/Month/Year Filed)

☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

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(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

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(Status)  
(patented, pending, abandoned)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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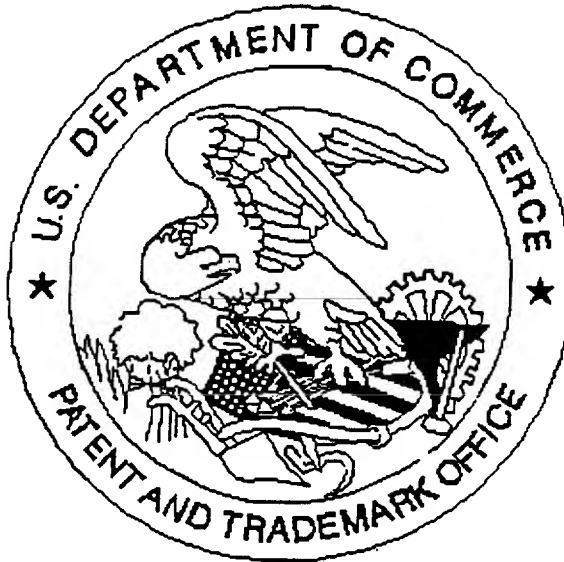
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| Citizenship                         |      |
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| Sixth inventor's signature          | Date |
| Residence                           |      |
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